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**Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR)  
Reporting : An Interrupted Time Series Analysis**

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Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration  
Rate (eGFR) Reporting:

An interrupted time series analysis

Ayub Akbari

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## Abstract

**Objectives:** To update a Cochrane review of interventions to improve outpatient referral and to assess changes in referrals to nephrologists after initiating automatic estimated glomerular filtration rate (eGFR) reporting.

**Methods:** Systematic review using standardized Cochrane methods. Before and after study with interrupted time series analysis using data from retrospective chart review on referrals from family medicine to nephrology.

**Results:** Review added one new study and removed one for total of 17 studies. Referrals improved with education and structured referral sheets. Of 2766 eligible referrals for one-year pre-eGFR reporting to one-year post, 96.6% were reviewed. There was a 68.2% increase in referrals for chronic kidney disease ( $P < 0.01$ ) and a 64.1% increase in total appropriate referrals ( $P = 0.01$ ) with no significant change in proportion of appropriate referrals (-2.5%,  $P=0.56$ ).

**Conclusion:** Systematic review findings did not change from the previous review. eGFR reporting increased both appropriate and inappropriate referrals.

## Contributors

**Contributors to the manuscript “Interventions to improve outpatient referrals from primary care to secondary care” presented in chapter 2.**

**Ayub Akbari (Masters candidate):** The candidate updated a previously published Cochrane review (Grimshaw JM, Winkens RA, Shirran L, et al. Interventions to improve outpatient referrals from primary care to secondary care. Cochrane Database Syst Rev 2005:CD005471). For the update, **AA** and Alain Mayhew (AM) screened identified citations and Jeremy Grimshaw (JG) was involved in the final selection. Data abstraction was done by **AA**, AM and Manal Alawi Al-Alawi (MA). **AA** and AM revised the original manuscript for the inclusion of new data.

**Contributors to the manuscript “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis” presented in chapter 3.**

**Ayub Akbari (Masters candidate):** Conceptualized the study, designed the study, wrote the protocol, developed the data collection form, piloted the data collection form, randomly audited data collection, randomly audited data entry, cleaned the data, performed the data analysis and wrote the manuscript.

**Jeremy Grimshaw (Thesis supervisor):** Provided expert opinion throughout the study and commented on the final manuscript.

**Dawn Stacey (Thesis supervisor):** Provided expert opinion throughout the study and commented on the final manuscript.

**Marcella Cheng-Fitzpatrick (Research assistant):** Helped with development of the data collection form, piloted the data collection form, collected the data and entered the data into excel spreadsheet.

**Tim Ramsay (Biostatistician):** Provided expert opinion on analysis of the data.

**William Hogg (Family Physician):** Was involved in the initial design of the study.

**Peter Magner (Nephrologist):** Was involved in the initial design of the study and provided guidance on appropriateness of referral.

**Robert Bell (Nephrologist):** Was involved in the initial design of the study.

**Jolanta Karpinski (Nephrologist):** Was involved in the initial design of the study.

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# Chapter 1

## Introduction

In many health care systems, family physicians are the first contact point for patients (1). They play a central role in providing care to the population. Family physicians consult specialists for several reasons including to clarify diagnosis, to perform a procedure, to provide specialized treatment and/or to reassure patients or the family physician on current approach to diagnosis and management (2). There is considerable variation in the referral process (3-6) indicating some patients who need referral are not being referred where as some patients who do not need referral get referred to the specialist. Management of patients with chronic kidney disease (CKD), that affects 11% of the population (7), is one example of this need for interchange between primary and specialty care. However, given it's chronic nature with progressive symptoms there is often concern about the appropriate timing of referrals in the disease trajectory that results in both under and over referrals.

In 2006, Ontario laboratories changed the way kidney function is reported by initiating estimated glomerular filtration rate (eGFR) reporting to improve the recognition of CKD (appendix 1). A study found that eGFR reporting was associated with an increase of 24% (95% confidence interval: 16%, 31%) referrals to nephrology (8). However, the study did not explore the appropriateness of these referrals to determine if the increase improved diagnosis of patients with moderate to severe CKD or inappropriately identified patients with milder forms of CKD that could be managed in primary care.

Despite that CKD is a common health issue, little is known about ways to improve this referral process. In a systematic review by Grimshaw and colleagues (9), none of the 17 studies evaluated referral of patients from primary care to nephrologists and few of the included studies were well conducted.

Therefore, the purpose of this thesis was to update the systematic review on interventions to improve referrals from primary care to secondary care and to assess changes in referrals to nephrologists after eGFR reporting.

## **Background and Review of the Literature**

### **1.2 Chronic Kidney Disease**

#### **1.2.1 Terminology of chronic diseases of the kidney**

Historically, various terms have been used to describe chronic problems occurring with the kidney including *generic* terms such as renal impairment, chronic renal failure, CKD and kidney injury and *etiological* terms such as glomerulonephritis, interstitial disease of the kidney, hypertensive kidney disease. In 2002, Kidney Disease Outcomes Quality Initiative (KDOQI) (10) based in United States harmonized these terms and suggested that chronic problems of the kidney should be indicated by the term “CKD”.

### 1.2.2 Definition of chronic kidney disease

Until 2002 there was also lack of agreement on the definition of CKD. An elevation in blood concentration of creatinine (a substance produced by the muscle and excreted by the kidneys) was the cornerstone of diagnosing kidney disease. Due to mounting evidence that creatinine was not a reliable marker for diagnosis of kidney disease (11-13), KDOQI defined CKD as “either kidney damage or glomerular filtration rate (GFR)  $<60$  ml/min/1.73m<sup>2</sup> for  $\geq 3$  months”(10). Since then many international organizations have adopted this definition (14-17). GFR is defined as the rate at which plasma is filtered through the glomeruli of the kidney (10). Blood entering the kidney passes through small blood vessels which then form tufts of capillaries (glomerular capillaries) connected to tubules. The proximal portion of the tubules is a cup like structure called Bowman’s capsule. The tuft of capillaries and the Bowman’s capsule is called the glomerulus. There are about one million glomeruli in each kidney. Due to pressure difference between the capillaries and the Bowman’s space, plasma gets filtered into the Bowman’s space, travels down the tubules where it is modified so that only substances that need to be excreted are left in the tubules which finally drain into the outside world (urine). Renal replacement therapy (for kidney failure) is usually required when end stage renal disease occurs and this is defined as GFR of less than 15 ml/min/1.73m<sup>2</sup> of body surface area (10). The GFR has traditionally been corrected for body surface area of a person as normal GFR is dependent on kidney size which is proportional to the body surface area of the individual.

### **1.2.3 Measurement of glomerular filtration rate for detection of kidney disease**

An ideal marker of GFR would be an endogenously produced substance which is produced at a constant rate, is freely filtered by the glomeruli of the kidney, is not secreted, reabsorbed or metabolized by the kidney or the urinary tract and would appear unchanged in the urine (13). Such a substance has not been detected as yet. Inulin is an exogenous substance that has these properties and as such the gold standard for measuring GFR of the kidney is inulin clearance (18). To measure GFR by inulin clearance, inulin is infused into the blood stream to achieve a constant plasma level. After achieving a constant plasma level, urine is collected over a defined period of time. The formula “Urine concentration of inulin x volume of urine per unit time/plasma concentration of inulin” (formula for clearance) is used to calculate the inulin clearance which equals GFR (18). As this procedure is quite cumbersome, in order to determine accurate GFR (usually in research settings) many other techniques such as radio isotope clearance of different molecules which are excreted by the kidneys (such as Technetium DTPA) have been developed which provide accurate measurements of GFR (18). None of this methodology is practical for routine measurement and monitoring of GFR in clinical setting as they are invasive, costly and time consuming (18). Endogenously produced substances that are filtered by the kidney and not reabsorbed or secreted into the bloodstream are useful for estimation of GFR (13). Creatinine, is one such substance.

Traditionally primary care providers had relied on the serum creatinine blood test to assess renal function (11-13, 19). However, serum creatinine concentration is not only

dependent on kidney function, but also on the rate of generation of creatinine, which is a function of a person's muscle mass (13). Women and the elderly have lower muscle mass and lower creatinine generation than young males, and their serum creatinine concentration is thus lower for the same degree of kidney function (20). Swedko et al. investigated the accuracy of serum creatinine in elderly (age  $\geq 65$  years) and found that serum creatinine is a flawed test for screening of CKD; as it overestimated the true kidney function in many female and elderly patients (11, 20). Serum creatinine is also insensitive in diagnosing kidney disease as patients may lose 50% of their GFR before serum creatinine would rise above the upper limit for normal (21).

In order to overcome the limitations of serum creatinine for determination of GFR, 24 hour creatinine clearance (requiring collection of urine for 24 hours) was used traditionally for measurement of GFR. However 24 hour creatinine clearance was found to substantially over estimate GFR at low true GFR as well as was found to be prone to collection errors and cumbersome for patients (18).

Recently simple mathematical formulae which rely on serum creatinine have become important in estimating GFR in routine clinical setting. Simple mathematical formulae, such as the Cockcroft-Gault formula (22) and the Modification of Diet in Renal Disease (MDRD) formula (23), can reliably estimate GFR from serum creatinine. They have been extensively validated in many populations, including the elderly, and have been found to reliably predict the GFR especially when the GFR is less than  $60 \text{ ml/min/1.73m}^2$  (which is a clinically significant depression of kidney function). Akbari et al. (24) and Wyatt et al. (25) have reported that laboratory reporting of eGFR improves the detection of CKD. Based

upon GFR, KDOQI not only defined CKD but also classified it into 5 stages depending on the severity of reduction of GFR (10). These five stages are shown in table 1.

**Table 1. Stages of Chronic Kidney Disease**

Stages	Description	GFR (ml/min/1.73m <sup>2</sup> )
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure (or dialysis)	≤15

#### **1.2.4 Prevalence, clinical importance and prognosis of chronic kidney disease**

Recent evidence suggests that CKD is very common. US data from the Third National Health and Nutrition Examination survey indicate that 11% of US adults suffer from CKD (26). In Canada about 1.5 million people are affected by CKD (27). The cost of renal replacement therapy is high (28), and treatment is associated with significant mortality and loss of quality of life (29). Over the last decade, the prevalence of End-Stage Renal Disease (ESRD) has increased by 7% annually and by the year 2005, an estimated 33,000 Canadians were on renal replacement therapy. At the same time new evidence in the last 10 years indicates that patients with abnormal renal function are at high risk of cardiovascular morbidity and mortality and that most patients with abnormal kidney

function will die from cardiovascular disease before reaching end stage renal disease (30, 31). Patients who survive usually have gradually declining renal function till they reach end stage renal disease. Major risk factors for progressing to end stage renal disease are: 1) Progressive decline in kidney function; 2) Hypertension; and 3) Proteinuria greater than 1 gram/day (32-35). Currently, there is no consensus on definition of progressive decline in kidney function. Kidney Health Australia defined it as 15% decline in eGFR over 3 months (36). National Institute for Health and Clinical Excellence in UK defined it as a decline in eGFR of more than 5 ml/min/1.73 m<sup>2</sup> within 1 year, or more than 10 ml/min/1.73 m<sup>2</sup> within 5 years (17). Canadian Society of Nephrology did not define progression but left it open to interpretation by local nephrologists (14). Ottawa nephrologists defined it as a decline of eGFR by > 20% over one year (appendix 1 and 2).

#### **1.2.5 Benefits of diagnosing chronic kidney disease earlier**

Progressive CKD leads to gradual reduction in kidney function and renal replacement therapy is usually required at eGFR below 15 ml/min/1.73m<sup>2</sup>(37). Blood pressure control and therapy with medications which block the renin angiotensin system such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers have shown to delay progressive loss of kidney function (28, 33, 38-47). Earlier diagnosis of CKD leads to effective therapies being instituted in a timely manner (25). Earlier diagnosis of CKD also has the benefit of prolonging kidney life much more than if CKD is diagnosed late. For example if CKD is diagnosed when GFR is 50 ml/min/1.73m<sup>2</sup> and the loss of kidney function is occurring at about 10 ml/min/yr (in a diabetic patient with uncontrolled blood

pressure and heavy proteinuria) (48-50). This patient would reach end stage renal disease (eGFR < 15 ml/min/1.73m<sup>2</sup>) in 3.5 years. Instituting therapy (blood pressure control and utilizing angiotensin converting enzyme inhibitors and angiotensin receptor blockers to decrease proteinuria) would decrease the loss of GFR to 5 ml/min/yr (51) which would lead to the patient reaching end stage renal disease in 7 years, gaining 3.5 years of kidney life. In the same patient diagnosing and instituting therapy at GFR of 30 ml/min/1.73m<sup>2</sup> would gain kidney life by only 1.5 years.

#### **1.2.6 Reporting of estimated Glomerular filtration Rate (eGFR) for earlier diagnosis of chronic kidney disease**

Reliance on serum creatinine to diagnose CKD is associated with under recognition of CKD as well as late referral to nephrologists (13, 19, 20, 52-58). Akbari et al. and Curtis et al. have shown that automatic reporting of eGFR in a primary care setting improves detection of CKD (24, 28). Several international organizations {American Society of Nephrology (10, 15) (in 2002), Australasian Creatinine Consensus Working Group (in 2005) (33), The Renal Association in UK (16) (in 2005), Canadian Society of Nephrology (14) (in 2006)}, have recommended that laboratories automatically calculate eGFR when physicians request a serum creatinine and report eGFR to physicians.

Community laboratories in Ontario since March 2006 have been reporting eGFR by the abbreviated MDRD formula, whenever serum creatinine is requested. This was a new test for the primary care providers and an educational initiative was undertaken by the laboratories in the form of mailing written material in November 2005 in preparation for

eGFR reporting (appendix 1). The nephrologists in Ottawa also developed an algorithm based on eGFR which was mailed to all the family physicians in the Ottawa area in March 2006 (appendix 2). In addition the nephrologists provided educational sessions (lectures and workshops) regarding interpretation of eGFR and referral to nephrology on an ad hoc basis to family physicians. This was a major initiative on the part of laboratories and academic nephrologists in Ottawa to improve detection and referral of CKD.

### **1.2.7 Concerns regarding eGFR reporting regarding inappropriate referral to nephrologists**

Reporting of eGFR was undertaken based on the evidence that reporting of eGFR was associated with improved detection of CKD and better management (24, 25). eGFR not only identifies patients with severe CKD (eGFR <30 ml/min/1.73m<sup>2</sup>, KDOQI stage 4 and 5) but also patients with mild to moderate CKD (eGFR ≥30 ml/min/1.73m<sup>2</sup>). With increased detection of CKD, there was a concern that referral of mild to moderate CKD without significant proteinuria (which can be managed by primary care physicians) would increase despite educational interventions. Increase of inappropriate referrals would have major impact on health care delivery as scarce resources would be spent on patients with relatively mild disease. It also would likely increase wait time for all nephrology referrals and would have financial impact on the system as specialist care is more costly than primary care. Due to this concern, the position papers by international organizations not only recommended automatic reporting of eGFR whenever a serum creatinine was

requested but also provided guidelines on which patients should be referred to nephrologists (14, 15, 59).

### **1.2.8 Recommendations of Canadian Society of Nephrology for referral of patients to nephrologists**

Canadian Society of Nephrology recommended referral to nephrologists (14) in patients who meet the following criteria:

- a. acute Kidney Failure
- b. eGFR <30 ml/min/1.73m<sup>2</sup>. (CKD stage 4 and 5)
- c. progressive decline of eGFR
- d. Urine protein/creatinine ratio (PCR) > 100 mg/mmol (approximately 900 mg/24 hours) or urine albumin to creatinine ratio (ACR) > 60 mg/mmol (approximately 500 mg/24 hr)
- e. If the practitioner is unable to achieve treatment targets for blood pressure or is unable to maintain the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers or other renal protective or cardiovascular protective strategies, or feels otherwise sufficiently unprepared to manage the CKD patient.

### **1.2.9 Literature regarding effect of automated eGFR reporting on referral patterns to nephrology**

Three studies have assessed referral patterns to nephrology after automated eGFR reporting. Noble et al. (60) evaluated the impact of eGFR reporting on outpatient referrals to a tertiary care and regional renal service and a single private practice 3 months prior to and 12 months post introduction of eGFR reporting. Appropriateness of referral to nephrology was assessed by Kidney Check Australia Taskforce criteria (KCAT) (36). During the entire study period, an education initiative was undertaken by KCAT for general practitioners and hospital staff and included lectures, accredited workshops, articles in primary care journals, addenda to pathology reports, online learning, mailed information leaflets, printed office materials and decision support systems embedded in medical software (60). During the study period a total of 1002 patients over 18 years of age were referred. They found that automated reporting of eGFR was associated with overall increase in referrals. Monthly referrals increased by 40%. The appropriateness of referral fell significantly from 74.3 % (pre-eGFR reporting) to 65.2% post-eGFR reporting but the absolute number of appropriate referral by KCAT criteria increased from 15 per month to 24 per month. For appropriateness of referral they also report incident rate ratio (0.63, confidence interval: 0.48, 0.82;  $P < 0.05$ ). Noble et al. only assessed appropriateness of referrals 3 months prior to intervention thus their pre-intervention data are quite limited and would not be able to take into account any seasonal variations (example, when

physicians take vacations). The total number of referrals prior to intervention was also quite limited at 171. Moreover they only had a total of 690 referrals from primary care. They performed their analysis on referrals from all sources rather than just primary care which gives us limited insight on referral patterns by primary care. Their data also indicate that no patients were referred to nephrology services for rapidly declining kidney function (fall in eGFR level of 15% over 3 months as defined by Kidney check Australia task force) and only two were referred in the 12 month post-intervention period which is insufficient for assessing referral secondary to progressive kidney disease. They utilized Poisson regression to model their data. Time series data are typically autocorrelated and therefore violates the independence assumption of Poisson regression. They also report *P*-value for the difference in proportion for appropriate referrals which again is inappropriate given the lack of independence in the data.

Richards et al. (61) assessed referral patterns to nephrology in U.K. in a wider study evaluating the impact of population-based identification of CKD using eGFR reporting. The study was conducted in the West Lincolnshire primary care trust in United Kingdom which has a population of 185,434 aged greater or equal to 15 years. There was an equivalent of one full time nephrologist for 40 practices (109 general practitioners) and 31 practices took part in the program. A disease management program was established two weeks after eGFR reporting. The disease management program was delivered by community nurses, dietician and social workers with the objectives of automated identification of patients with CKD, patient education and appropriate referral to nephrology. At six months of eGFR

reporting a referral assessment service was initiated as part of the disease management program to ensure guidelines for nephrology referrals were followed. They calculated 3 month rolling average (interrupted time series design) and determined that there was a 2.7 times increase in referrals in the first six months of eGFR reporting (prior to referral assessment service which enforced adherence to guidelines for referral) compared to 11 months prior to eGFR reporting. Subsequent to establishment of referral assessment service, there was a decline in referrals but it remained elevated at 1.5 times pre-eGFR reporting. They report that patients referred were more appropriate for a specialist service. It is unclear from their report how appropriateness of referral was determined and whether there was a difference in appropriateness of referral pre and post-eGFR reporting.

Jain et al. (8) undertook a large administrative database study in Ontario, Canada to determine the impact of eGFR reporting on referrals to nephrology. This study utilizing autoregressive integrated moving average model (ARIMA), compared 84 months (January 1999 to December 2005) of pre-eGFR reporting data to 21 months (January 2006 till September 2007) post-eGFR reporting data. Jain et al. report a 24% (95% confidence interval: 16%, 31%) increase in referrals to nephrology post-eGFR reporting. This study also reports that the major increase in referrals post-eGFR reporting was for women, 39% (95% confidence interval: 28%, 51%) and the elderly (age  $\geq$  80 years), 57.8% (95% confidence interval: 35.3%, 80.2%). Jain et al. did not explore appropriateness of referrals.

Despite that introduction of eGFR reporting in Ontario was associated with an increase in referrals to nephrology little is known about the characteristics of these

referrals including appropriateness (8). The other two studies, conducted in the UK and AU (60, 61), that attempted to explore appropriateness of referral to nephrology post-eGFR were limited by the number of referrals included, limited length of referral period studied, and limitations in the use of statistical technique.

#### **1.2.10 Literature regarding interventions to improve referral to specialists**

Grimshaw et al. conducted a systematic review of the literature regarding interventions to improve referral to specialists (9). This review included literature till February 2002. The objective of the review was “to estimate the effectiveness and efficiency of interventions to change outpatient referral rates or improve outpatient referral appropriateness.” They electronically searched the Cochrane Effective Practice and Organization of Care (EPOC) register and National Research register. Included articles had to specify that influencing referral was a primary objective of the intervention and the design of the study had to be randomized controlled trials, controlled clinical trials, controlled before and after studies or interrupted time series. Interventions to change or improve referrals for open access radiological or laboratory diagnostic investigations were excluded. Seventeen studies met the inclusion criteria for the review. Nine studies evaluated professional educational interventions, three studies evaluated organizational intervention and five studies evaluated financial interventions. In this review Grimshaw et al. found that active local educational interventions involving secondary care specialists and structured referral sheets were the only interventions for which evidence was available to impact on referral rates. However, none were conducted on referrals to nephrology.

### **1.3 Rationale for the current study**

Late referral to nephrology has been associated with increased mortality and morbidity. In order to improve earlier referrals, several guidelines were published by the nephrology community with limited impact. Although eGFR reporting improves detection of CKD, the data on its impact on appropriate referral to nephrology is limited. In order to determine the impact of a major change in reporting of laboratory test of kidney function along with real life educational activities, we conducted this study with the primary objective of comparing appropriateness of referrals to nephrology from family doctors pre and post-eGFR reporting. The data from this study would help to determine whether changing laboratory reporting for diagnosis of CKD and real life education improved referral patterns to nephrology or was associated with an increase in inappropriate referrals with its attendant consequences.

In addition, to explore the recent literature on improving the referral process, we updated the systematic review “Interventions to improve outpatient referrals from primary care to secondary care” conducted by Grimshaw et al. and last published in *Cochrane Database of Systematic Reviews 2005, issue 3 (9)*.

We present this thesis in manuscript format. The review “Interventions to improve outpatient referrals from primary care to secondary care” is presented in chapter 2. In chapter 3 we present the manuscript “Change in Referral Patterns to Nephrologists after

eGFR Reporting: An interrupted time series analysis". In chapter 4 we present an overarching discussion.

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# Chapter 2

## Interventions to improve outpatient referrals from primary care to secondary care (Review)

This review is published as a Cochrane Review in the *Cochrane Database of Systematic Reviews* 2008, Issue 3. Cochrane Reviews are regularly updated as new evidence emerges and in response to comments and criticisms, and the *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the Review.’ Interventions to improve outpatient referrals from primary care to secondary care (Review). Akbari A, Mayhew A, Al-Alawi MA, Grimshaw JM, Winkens RAG, Glidewell E, Pritchard C, Thomas R, Fraser C *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD005471. DOI: 10.1002/14651858.CD005471.

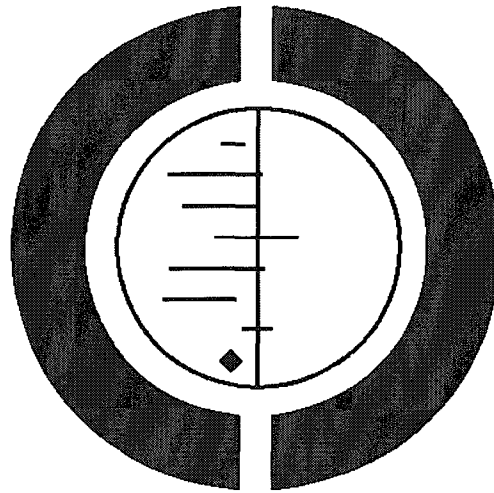
<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005471/frame.html>

### Contribution of Authors:

RW and JG developed the review protocol. CF developed the EPOC search strategy and additional Medline search strategies. EG undertook electronic searches. EG, JG, CF, CP and RW selected studies for inclusion in the review. EG, JG, RW, AM, CP and RT undertook data abstraction. JG drafted the paper. EG, CF, RW and RT commented on all drafts of the paper. For the update, AA and AM screened identified studies and JG was involved in the final selection. Data abstraction was done by AA, AM and MA.

# Interventions to improve outpatient referrals from primary care to secondary care (Review)

Akbari A, Mayhew A, Al-Alawi MA, Grimshaw JM, Winkens RAG, Glidewell E, Pritchard C,  
Thomas R, Fraser C



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# Interventions to improve outpatient referrals from primary care to secondary care (Review)

Akbari A, Mayhew A, Al-Alawi MA, Grimshaw JM, Winkens RAG, Glidewell E, Pritchard C, Thomas R, Fraser C

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## ABSTRACT

**Background:** The primary care specialist interface is a key organisational feature of many health care systems. Patients are referred to specialist care when investigation or therapeutic options are exhausted in primary care and more specialised care is needed. Referral has considerable implications for patients, the health care system and health care costs. There is considerable evidence that the referral processes can be improved.

**Objectives:** To estimate the effectiveness and efficiency of interventions to change outpatient referral rates or improve outpatient referral appropriateness.

**Search strategy:** We conducted electronic searches of the Cochrane Effective Practice and Organisation of Care (EPOC) group specialised register (developed through extensive searches of MEDLINE, EMBASE, Healthstar and the Cochrane Library) (February 2002) and

the National Research Register. Updated searches were conducted in MEDLINE and the EPOC specialised register up to October 2007.

**Selection criteria:** Randomised controlled trials, controlled clinical trials, controlled before and after studies and interrupted time series of interventions to change or improve outpatient referrals. Participants were primary care physicians. The outcomes were objectively measured provider performance or health outcomes.

**Data collection and analysis:** A minimum of two reviewers independently extracted data and assessed study quality.

**Main results:** Seventeen studies involving 23 separate comparisons were included. Nine studies (14 comparisons) evaluated professional educational interventions. Ineffective strategies included: passive dissemination of local referral guidelines (two studies), feedback of referral rates (one study) and discussion with an independent medical adviser (one study). Generally effective strategies included dissemination of guidelines with structured referral sheets (four out of five studies) and involvement of consultants in educational activities (two out of three studies). Four studies evaluated organisational interventions (patient management by family physicians compared to general internists, attachment of a physiotherapist to general practices, a new slot system for referrals and requiring a second 'in-house' opinion prior to referral), all of which were effective. Four studies (five comparisons) evaluated financial interventions. One study evaluating change from a capitation based to mixed capitation and fee-for-service system and from a fee-for-service to a capitation based system (with an element of risk sharing for secondary care

services) observed a reduction in referral rates. Modest reductions in referral rates of uncertain significance were observed following the introduction of the general practice fundholding scheme in the United Kingdom (UK). One study evaluating the effect of providing access to private specialists demonstrated an increase in the proportion of patients referred to specialist services but no overall effect on referral rates.

**Authors' conclusions:** There are a limited number of rigorous evaluations to base policy on. Active local educational interventions involving secondary care specialists and structured referral sheets are the only interventions shown to impact on referral rates based on current evidence. The effects of 'in-house' second opinion and other intermediate primary care based alternatives to outpatient referral appear promising.

## PLAIN LANGUAGE SUMMARY

Are there effective methods to improve the process of referring patients to specialised care?

Patients are referred to a specialist when more specialised care is needed. It has however been shown that the process by which patients are referred could be improved. Some patients may be referred to a specialist inappropriately or not be referred when they should have, or when they were referred have unnecessary tests or procedures. This review found 17 studies that evaluated whether educating health care professionals about referrals, changing the organisation or system of referrals, and changing the fees or payments for referrals, could improve the referral process.

**Education:** The referral process will most likely improve when guidelines for referral are distributed with standard referral forms and when the health care professionals who are the consultants are involved in teaching about referring. But simply distributing guidelines and providing health care professionals with feedback about how they are referring may not improve the process.

**Organisation:** There is little evidence about organisational changes. But providing a second opinion before referring, or enhancing the services provided before a referral (e.g. providing access to a physiotherapist) may improve the referral process.

**Financial:** There is not enough evidence to draw firm conclusions about financial changes. Financial changes can change the number of referrals but it is not known whether they improve the quality or appropriateness of referrals.

## BACKGROUND

The primary-secondary care interface is a key organisational feature of many health care systems. Primary care physicians provide primary health care and act as 'gatekeepers' with responsibility for defining which patients require secondary care. The referral system is the 'organisational structure for referring medical problems from generalists to specialists' (Coulter 1993). Some countries have a similar formal referral system, for example Denmark, the Netherlands and the UK, where primary care physicians provide health care and act as gatekeepers with responsibility for defining which patients require specialist care. Other countries have a less formalised referral system, for example France, Germany and the United States of America (USA) (Casparie 1988; Gervas 1994; Marinker 1988; Roland 1992).

Patients are referred to specialist care to obtain advice on diagnosis or management, to obtain a specialised procedure when investigation or therapeutic options are exhausted in primary care and more specialised care is needed, and to obtain a second opinion. During referral, there is 'a transfer of responsibility for some aspect of the patient's care' from primary to secondary care (McWhinney 1989). Referral has considerable implications for patients, the health care system and health care costs. However, there is considerable evidence that the process of referral is sub optimal. There are unexplained variations in referral rates (Wilkin 1992), suggesting that some patients are referred inappropriately, consuming health care resources which could have been used to provide other services, and that some patients are inappropriately managed in primary care settings who would

benefit from specialist care. There is also evidence of inappropriateness of referral and poor communication at the time of referral (Roland 1992). As a result, patients may undergo unnecessary diagnostic or therapeutic procedures (including hospitalisation). Despite the growing awareness of problems associated with referrals, there has been relatively little research evaluating interventions to improve referral behaviour compared with other types of behaviour (for example, prescribing). A systematic review of studies evaluating professional interventions to improve referral behaviour identified only four studies published between 1966 and 1995 (Grimshaw 1998). Mixed results were found; training plus structured assessment cards and joint consultation sessions were effective. However, development and dissemination of local consensus guidelines and the introduction of fundholding in UK primary care were found to have little effect. The review concluded that it was difficult to draw firm conclusions as a result of the limited number of rigorous studies identified and that further research was needed on interventions to improve the referral process. Since that review was undertaken, the NHS (Primary and secondary care interface programme) in the UK and other funders have commissioned a number of further studies. This is an updated version of the Cochrane review published in 2005 (Grimshaw 2005).

## **OBJECTIVES**

The aims of the review were:

- (1) To identify which interventions have been evaluated to change primary care outpatient referral rates or improve referral appropriateness.
- (2) To estimate the effectiveness of interventions to change primary care outpatient referral rates or improve outpatient referral appropriateness.

## **CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

### **Types of studies**

Randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs) and interrupted time series (ITs).

### **Types of participants**

Primary care physicians, defined broadly as any medically qualified physician who provides primary health care. Primary health care provides 'integrated, easy to access, health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained and continuous relationship with patients, and practising in the context of family and community' (Vanselow 1995). Primary care physicians include general practitioners, family doctors, family physicians, family practitioners and other physicians working in primary health care settings who fulfil primary health care tasks (for example, general paediatricians in the USA).

Specialist physicians working in hospitals or community outpatient settings.

## **Types of intervention**

The review focused on interventions to change outpatient referral rates or improve outpatient referrals appropriateness. During outpatient referral, there is 'a transfer of responsibility for some aspect of the patient's care' from primary to secondary care (McWhinney 1989). Referral is a management option in most diseases, therefore any intervention aiming to influence clinical behaviour could have indirect effects on the quality and quantity of referrals. Studies had to report explicitly that influencing referral was a primary objective of the intervention to be included.

Interventions were classified according to the Cochrane EPOC taxonomy of interventions (see SCOPE in GROUP DETAILS).

Interventions to change or improve referrals for open access radiological or laboratory diagnostic investigations (e.g. radiology) were excluded.

## **Types of outcome measures**

Objectively measured provider performance in a health care setting (for example, referral rates or appropriateness of referral) or health outcomes were included.

## **SEARCH METHODS FOR IDENTIFICATION OF STUDIES**

See: Cochrane Effective Practice and Organisation of Care Group methods used in reviews.

### **(1) Cochrane Effective Practice and Organisation of Care Register**

For the original review, we searched the specialised register and pending register of the Cochrane Effective Practice and Organisation of Care group using the terms: refer\* and

consultation\* with the term outpatient\*. The register is based upon retrospective and prospective sensitive searches of key bibliographic databases (including MEDLINE and CINAHL), hand searching of key journals and reference lists of published literature reviews (see SEARCH STRATEGIES FOR THE IDENTIFICATION OF STUDIES under GROUP DETAILS). Potentially relevant studies are entered into the pending register for assessment of the full text articles. Studies are included in the specialised register if they use RCT, CCT, CBA or ITS designs and evaluate interventions within EPOC's scope. Studies in the specialised register are coded by their design, type of intervention and type of targeted behaviour and include the full MEDLINE, EMBASE or Healthstar reference. The register was searched on February 2002 by the EPOC TSC for the initial version of the review. For the update, the EPOC register was searched up to October 2007 (refer to Appendix 01).

## **(2) MEDLINE**

For the initial review, we conducted additional test searches of MEDLINE using a search strategy developed by CF. However, a search of the MEDLINE 1995 to 1999 database identified 6,000 records (after records identified by the existing EPOC search strategy were excluded). No additional potentially relevant studies were identified when we screened the first 500 records. As a result, we did not undertake further MEDLINE searches.

For this update, Medline was searched using the following search strategy:

Database: Ovid MEDLINE(R) <1950 to October Week 1 2007>

Search Strategy:

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- 1 Family Practice/st (3894)
- 2 Primary Health Care/st (3454)
- 3 Physicians, Family/ (11246)
- 4 ((general or family) adj practi\$.tw. (49353)
- 5 family physic\$.tw. (7470)
- 6 primary care.tw. (38351)
- 7 primary health care.tw. (8717)
- 8 (gp or gps).tw. (21831)
- 9 exp Specialties, Medical/ (369884)
- 10 specialist?.tw. (33613)
- 11 Physician's Practice Patterns/ (23725)
- 12 ((secondary or speciali?ed) adj care).tw. (2153)
- 13 or/1-12 (483483)
- 14 \*"Referral and Consultation"/ (13844)
- 15 (referral? adj2 (practice? or rate? or appropriateness or improve\$ or appropriate\$ or method? or process\$ or accuracy or pattern?)).tw. (4561)
- 16 \*Gatekeeping/ (180)
- 17 gatekeeper\$.tw. (1305)
- 18 (outpatient? adj3 referral?).tw. (417)
- 19 or/14-18 (18547)

20 referral?.tw. (37828)  
21 13 and 19 and 20 (3532)  
22 randomized controlled trial.pt. (244391)  
23 random\$.tw. (389305)  
24 intervention?.tw. (255306)  
25 control\$.tw. (1596990)  
26 evaluat\$.tw. (1257209)  
27 effect?.tw. (2522982)  
28 or/22-27 (4629321)  
29 21 and 28 (1469)  
30 animal/ (4220069)  
31 human/ (10034045)  
32 30 not (30 and 31) (3194259)  
33 29 not 32 (1469)  
34 limit 33 to yr="1999 - 2007" (924)

### **(3) UK National Research Register**

We searched the UK National Research Register with the terms: (outpat\* and refer\*) and interface. We searched MEDLINE for published reports of completed projects by the name of the lead researcher.

### **METHODS OF THE REVIEW**

The review was conducted using standard EPOC methods (Bero 2008).

EG, CF, RT and CP screened the results of searches to identify potentially relevant papers.

AA and AM screened the results of the updated searches. Two difficulties arose when identifying potentially relevant studies:

**(1) Problems associated with definition of intervention** – We Identified many studies which reported the effects of interventions on referral rates, however the majority of these focused on the general management of a clinical condition rather than on referral. As in our inclusion criteria we only considered interventions if they explicitly reported that a primary objective was to influence referrals.

**(2) Problems associated with definition of primary care** – A significant number of potentially relevant studies were conducted in US ambulatory care clinics and it was difficult to determine whether the professionals targeted fulfilled our inclusion criteria. We contacted a number of experts in the US who advised us to consider family physicians and general internal medicine physicians as primary care physicians.

Two reviewers (EG and JG or CP or RT), independently selected the studies to be included in the review, and AA and AM selected studies for the update, with input from JG. A list of excluded studies can be obtained from the authors.

Data from each paper were abstracted independently by two authors (EG and at least one of CP, JG, AM, RT or RW) using the standard EPOC checklist (Bero 2008) and by three authors (AA, AM and MA) for the update. Data abstraction was checked and discrepancies were resolved through discussion by the relevant two authors. JG acted as arbiter for any

unresolved discrepancies. If one of the authors of this review was involved in one of the reviewed studies, they did not participate in the abstraction of that study.

Given the substantial heterogeneity of interventions and methods across studies, it was not sensible to use meta-analysis to pool the results of studies. Instead, we present the results of studies in tabular form and make a qualitative assessment of the effects of studies, based upon the quality, the size and direction of effect observed and the statistical significance of the studies. We report the following data (where available): pre intervention study and control data in natural units and statistical significance across groups, post intervention study and control data in natural units and statistical significance across groups, absolute and relative percentage improvement. If a unit of analysis error was present, we attempted to re-analyse the study using data provided in the original paper. If this was not possible, we present the point estimates of effects without p-values or 95% confidence intervals. If the study authors had stated the hypothesised direction of effect for any outcome variable, we noted whether the result favoured the study or control groups.

## **DESCRIPTION OF STUDIES**

See *Table of Included Studies*.

Seventeen studies were included in the original review, all but one study reported since 1990.

The search for the update identified 1058 hits, of which only 4 were considered potentially eligible. Upon further review, only one additional study from the updated searches met the inclusion criteria. One study (Krasnik 1990) from the original review was removed. Krasnik 1990 was a CBA with only one intervention and one control group, which does not meet the revised EPOC inclusion criteria for CBA studies.

### **Characteristics of participants**

Twelve included studies were based in the UK, two in the US and one each in the Netherlands, Palestine, and Finland.

### **Characteristics of the intervention**

Nine studies evaluated professional educational interventions (including 14 comparisons), four studies evaluated organisational interventions and four studies evaluated financial interventions (including five comparisons).

### **Professional education interventions**

Seven studies evaluated different methods of disseminating and implementing referral guidelines. Two evaluated passive dissemination of local guidelines (Jones 1993; Grimshaw 1998). Jones (Jones 1993) evaluated the effects of disseminating consensus guidelines for management and referral of patients with dyspepsia. Grimshaw (Grimshaw 1998) evaluated the effects of disseminating locally developed guidelines for four common tracer conditions (low back pain, menorrhagia, suspected peptic ulcer, varicose veins) that accounted for 8% of total referrals. Five studies evaluated dissemination of referral guidelines with structured referral sheets-checklists to be completed at the time of referral

prompting the primary care physician about important elements of pre-referral investigation and management (Abu-Ramadan 2002; Bennett 2001; Emslie 1993; Morrison 2001; Thomas 2003). Two of these focused on general practitioner management and referral of infertility: Emslie's study (Emslie 1993) was based in a relatively simple referral setting (one referral hospital, traditionally good links between local general practitioners and the hospital), whereas Morrison's study (Morrison 2001) was set in a more complex referral settings (five referral hospitals in large city setting). Thomas' study (Thomas 2003) evaluated the effects of a guideline based, open access investigation service for two common urological conditions. General practitioners could refer patients to a fast track investigation service if they used a structured letter based upon referral guidelines. Abu-Ramadan's study (Abu-Ramadan 2002) evaluated the effect of a multifaceted intervention involving educational meetings, a new referral and reply sheet, new staff and changes in equipment and facilities. Bennett (Bennett 2001) included a risk factor checklist and a training video to train the practitioners.

Three studies evaluated secondary care provider-led educational strategies (Banait 2000; Grimshaw 1998; Vierhout 1995). Vierhout's study (Vierhout 1995) evaluated the effects of joint general practitioner-consultant sessions for patients whose general practitioners were uncertain of diagnosis or management and were considering orthopaedic referral. The sessions were held monthly for 18 months; each of four orthopaedic surgeons saw patients with the same three general practitioners. Grimshaw (Grimshaw 1998) evaluated GP-consultant small group discussions for four common tracer conditions (see above). Banait

(Banait 2000) evaluated consultant-led education outreach visits to disseminate guidelines for the management and referral of patients with dyspepsia. Finally Grimshaw's study (Grimshaw 1998) also evaluated the effects of feeding back information about referral rate to general practitioners and discussions between general practitioners and an independent adviser about referral. Due to the complex design, Grimshaw (Grimshaw 1998) was able to explore the effects of the four interventions separately and in combination.

### **Organisational interventions**

Bertakis (Bertakis 1987) evaluated the effects of the primary care physician's discipline (general internal medicine versus family physician) on referral behaviour. O'Cathain (O'Cathain 1995) evaluated the effect of providing primary care based physiotherapy services on referrals to orthopaedics and rheumatology. Kinnersley (Kinnersley 1999) evaluated the effects of requiring an 'in house' second opinion prior to referral. General practitioners considering referral arranged for the patient to see a different partner in the same practice for an independent assessment. Bridgman 2005 evaluated the effect of a new system where the number of appointment slots was allocated based on the size of the practices.

### **Financial interventions**

Davidson (Davidson 1992) evaluated the effects of a change in remuneration system from a low cost fee-for-service system to either a high cost fee-for-service system or capitation-based budgetary system (with some degree of risk sharing by the provider for secondary care provision) for the management of Medicaid eligible paediatric care. Two UK based

studies evaluated the effect of fundholding on referral patterns (Coulter 1993, Kammerling 1996). Linnala (Linnala 2001) examined the impact of charging patients the same (lesser) rate to be seen by a private specialist as they would have been charged to see a hospital based specialist. All of the professional educational interventions focused on a single or a small number of tracer conditions whereas the organisational and financial interventions focused on a broader range of conditions and problems.

## **Methodological Quality**

### **Study designs**

Study designs included: eight cluster randomised trials (which randomised by professional or practice) (Banait 2000; Bennett 2001; Davidson 1992; Emslie 1993; Jones 1993; Kinnersley 1999; Morrison 2001; Thomas 2003); two patient randomised trials (Bertakis 1987; Vierhout 1995); one controlled clinical trial (which allocated by practice) (Grimshaw 1998); five controlled before and after studies (Bridgman 2005; Coulter 1993; Kammerling 1996; Linnala 2001; O’Cathain 1995) and one interrupted time series (Abu-Ramadan 2002).

### **Quality assessments (Bero 2008)**

There were eleven randomised or controlled clinical trials. Randomisation concealment was done in four of these studies and was not clear in the remaining seven studies.

Adequate follow up of providers (greater than 80%) was done in five studies. Blinded assessment of outcomes (protection against detection bias) was present in one study, was not clear in eight studies and not done in two studies. Baseline measurement was done

and no substantial differences were present across study groups in three studies, baseline measurement was not done or it was unclear whether there were significant differences across study groups in six studies and there were baseline differences likely to undermine the post intervention differences in two studies. Reliable outcomes were only used in three studies. Protection against contamination was done for nine studies, not clear for one study and not done for one study. Contamination could have occurred within the Vierhout (Vierhout 1995) study because participating general practitioners would have looked after both study and control patients.

There were five controlled before and after studies. Baseline measurement was reported and similar across study groups for one study, baseline measurement was not done or it was unclear whether there were significant differences across study groups in one study and there were baseline differences likely to undermine the post intervention differences in three studies. The characteristics of the second site were reported and similar for one study; it was not clear whether the characteristics of the second site were similar for the other studies. Follow up of providers was not specified in four studies (reported as NOT CLEAR) and not adequate (less than 80% follow up) in one study (reported as DONE).

Blinded assessment of outcomes was done for three studies and not done for two studies.

Reliable outcome measures were used in four studies and not clear in one study. All studies adequately protected against contamination.

There was one interrupted time series study. Abu Ramadan (Abu- Ramadan 2002) monitored referral rates from general practitioners to an eye hospital monthly for 18

months prior and 30 months following the intervention. The intervention was multifaceted and included a new referral and reply sheet, new group and self training of staff and a monitoring system to evaluate and provide advice. The only data reported is the number of referrals, so it is impossible to assess if the data set is complete. There are sufficient points to include the study, but no formal test for trend. The intervention is apparently solely targeted at referrals, but because it is multifaceted, it is difficult to assess what aspect of the intervention is effective.

### **Other methodological characteristics**

#### **Proportion of eligible providers participating in the study**

In eight studies, the majority of eligible providers participated in the study (Bennett 2001; Banait 2000; Davidson 1992; Emslie 1993; Jones 1993; Linnala 2001; Morrison 2001; Thomas 2003). In two studies less than 50% of the eligible providers were included (Coulter 1993; Grimshaw 1998). It was not clear what proportion of eligible providers participated in seven studies (Abu-Ramadan 2002; Bridgman 2005; Bertakis 1987; Kammerling 1996; Kinnersley 1999; O’Cathain 1995; Vierhout 1995). Only 12 general practitioners were involved in Vierhout’s study (Vierhout 1995).

#### **Types of outcomes reported**

Studies of professional educational interventions typically reported a combination of data relating to quantity of referrals, quality of referrals and other related outcomes (for example, impact on prescribing or subsequent hospital management). However, all but one

(Linnala 2001) of the studies of organisational and financial interventions only reported data on quantity of referrals.

### **Unit of analysis errors**

In cluster randomised trials, providers or groups of providers are randomised but data is collected at the patient level. A fundamental assumption of the statistics used to analyse patient-randomised trials is that the outcome for an individual patient is completely unrelated to that for any other patient - they are said to be 'independent'. This assumption is violated, however, when cluster randomisation is adopted, because patients within any one cluster are more likely to respond in a similar manner. The primary consequence of adopting a cluster randomised design is that it is not as statistically efficient and has lower statistical power than a patient-randomised trial of equivalent size. Because of this lack of independence, sample sizes require to be inflated to adjust for the clustering effect, and special analytic techniques, such as multilevel modelling need to be adopted, unless simple cluster-level analysis is undertaken. If patient level analyses using standard statistical tests are used, the results are likely to be over precise with artificially extreme p-values and over-narrow confidence intervals, increasing the chances of spuriously significant findings and misleading conclusions. This is known as a unit of analysis error. Unit of analysis errors were potentially present in six of the cluster randomised trials (Banait 2000; Bennett 2001; Davidson 1992; Emslie 1993; Jones 1993; Kinnersley 1999) and all but one (Bridgman 2005) of the controlled before and after studies.

### **Economic evaluation**

Only two studies conducted an economic evaluation (Morrison 2001; Thomas 2003).

## **RESULTS**

See Table 01.

### **Professional educational interventions**

Two studies evaluated passive dissemination of locally developed consensus referral guidelines and neither observed changes in quantity or quality of referrals (Jones 1993; Grimshaw 1998). Jones and colleagues (Jones 1993) evaluated the development and dissemination of management guidelines for dyspepsia. They hypothesised that the guidelines would lead to an increase in the use of endoscopy compared with barium meals, fewer investigations of younger patients and changes in prescribing patterns of H2-antagonists. They observed an increase in the number of referrals for upper gastrointestinal problems, referrals for endoscopy and upper gastrointestinal radiology investigations. Unfortunately, there was baseline imbalance for all of these outcomes which could undermine the post intervention differences. If differences in absolute change from baseline is considered, the direction of the observed effects support the authors' hypotheses. Unfortunately, because these outcomes also had unit of analysis errors which could not be re-analysed, the statistical significance of these findings is uncertain. There were statistically significant increases in prescribing costs for upper gastrointestinal drugs and ulcer healing drugs. The authors concluded that the guidelines 'acceptance and adoption was variable and their measured effects on some aspects of clinical behaviour

were relatively weak and not necessarily associated with either decreased costs or improved quality of care' (Jones 1993). Grimshaw (Grimshaw 1998) evaluated postal dissemination of referral guidelines for four tracer conditions; he observed no significant changes in referral patterns or appropriateness of referral.

Five studies evaluated dissemination of referral guidelines with structured management sheets and observed improved pre-referral management of patients (Abu-Ramadan 2002; Bennett 2001; Emslie 1993; Morrison 2001; Thomas 2003). Abu-Ramadan (Abu-Ramadan 2002) used an interrupted time series design to evaluate appropriate referrals for treatment of eye conditions. Prior to the implementation of the intervention, it was reported that general practitioners were not dealing with eye injuries and referring them too frequently. This resulted in increased workload for the ophthalmologists at the hospital, which in turn led to time limited consultations and increased expenses. Training programs were provided to 40 primary care physicians to educate them about screening, emergency issues and appropriate referrals. The trained physicians were then distributed to various sites to facilitate the teaching of the other practitioners. A new referral reply sheet was used, eye medications were made available and a monitoring, evaluating and advice system set up. The study reports an over 50% reduction in the number of referrals to the eye hospital post intervention. However, it is very difficult to interpret which aspect of the intervention contributed most to the change in the number of referrals.

Bennett (Bennett 2001) evaluated the use of a training video, checklist or both against a control group for referrals to specialists for otitis media with effusion (OME). There has

been a wide range of general practice variation in referral rates for this condition and there are concerns about both over referral and under referral. There was no effect of any of the interventions on the referral rates. However, the authors analyzed data from 68% of the practices to determine 'quality of referrals'. They examined the percentage of children who at the time they were seen by a specialist, had a hearing loss greater than 20 dB in the better ear (an accepted indication for referral). In the group of physicians who saw the video and had access to the checklist, the percentage of appropriate referrals increased following the intervention; in all other groups including the control group it decreased.

Emslie and colleagues (Emslie 1993) evaluated dissemination of guidelines for general practitioner management and referral of infertile couples in the Grampian region of Scotland. The guidelines were disseminated with an infertility management package which included a structured referral sheet. They observed improvements in: eliciting five items of sexual history (median improvement in post intervention absolute difference +16.0%); undertaking five pre referral examinations and investigations in the female partner (median improvement in post intervention absolute difference +24%); and undertaking two pre referral examinations and investigations in the male partner (median improvement in post intervention absolute difference +18%). There was also an increase in the number of referrals in which the male partner had been seen prior to referral (improvement in post intervention absolute difference +17%). Unfortunately there was a unit of analysis error and the statistical significance of these findings is unclear. Furthermore, data from study and control groups were collected by different methods; data about referrals made by

study general practitioners including the structured management sheet with the referral letter were abstracted from the referral document, whereas data from study general practitioners not using the structured referral document and control general practitioners were collected by computer assisted telephone interview.

Morrison and colleagues (Morrison 2001) evaluated a similar intervention in the Greater Glasgow Health Board area. They observed no difference in referral rates per 1000 registered women aged 20 to 44. There was little evidence of inappropriate referral; only 1.1% of patients were referred after less than 12 months of infertility without an indication for early referral. There were improvements in five items of pre-referral investigations/advice, with a median improvement in post intervention absolute difference of + 7.3%, but none of the improvements in individual tests were statistically significant. However there was a statistically significant improvement in the proportion of couples receiving all appropriate investigations/advice (improvement in post intervention absolute difference +9.6%, Odds ratio 1.324; 95%CI 1.001 to 1.752, p=0.025). Following referral, hospitals commonly repeated investigations (100% of patients with a normal midluteal progesterone and 34.5% of patients with a normal semen analysis as reported in the referral letter received repeat investigations in hospital). There were no differences in the time from first appointment to establishing a management plan or in the proportion of couples with a management plan after one year of referral. There were 8% fewer pregnancies within 12 months in the study group. General practice and hospital costs were greater in the study group (unfortunately there was a unit of analysis error and the

statistical significance of these findings is unclear).

Thomas and colleagues (Thomas 2003) evaluated the effect of a guideline based open access investigation service for two common urological conditions (prostatism and microscopic haematuria). Participating general practitioners were offered a two-hour educational meeting and were mailed a guideline package (including a guideline booklet, quick reference flowchart and structured referral checklists). Under the existing system, patients usually attended an initial outpatient appointment and at least one further appointment for routine day case investigations. The open access investigation service allowed doctors to refer patients directly for day case investigations using the guidelines. Patients attending the open access service had all routine hospital-based investigations and a management plan determined at this single consultation. Thomas and colleagues (Thomas 2003) hypothesised that the intervention would have little effect on general practitioners' referral patterns or patient outcomes, increase general practitioner compliance with referral guidelines, reduce patient waiting times, increase likelihood that patient would receive a management plan at first appointment and be discharged at 12 months. They observed that 48.2% of eligible patients were referred through the new system, freeing up the equivalent of 350 new outpatient slots over a 12 month period. There were no differences in referral patterns or case mix of the patients referred. Compliance with referral guidelines increased significantly. Waiting times for first appointments for the tracer conditions decreased (Ratio of means of waiting times 0.7 95% CI 0.55 to 0.89) although the post intervention difference is likely to underestimate the

true effect of the intervention as there was a substantial fall in waiting times for control patients probably as a result of the freed up new outpatient appointments. There was also a reduction in waiting times for all urology patients of 11 weeks (95% CI 7.1 to 15 weeks). The probability of patients receiving a management decision at first appointment increased significantly (Odds ratio 5.8; 95% CI 2.9 to 11.5). There was a non significant increase in the probability of discharge at 12 months (Odds ratio 1.7; 95% CI 0.92 to 3.27). The annual cost of the intervention was estimated to be £9555 (representing the total costs of guideline development and dissemination, however in many settings these costs would be subsumed into normal running costs). There were non-significant reductions in post referral general practice costs (for prostatism only) and the travel costs of patients attending health services. There were significant reductions in the mean hospital management costs per patient of £80.26 for prostatism and £44.79 for haematuria.

Two of the three studies (Banait 2000; Grimshaw 1998; Vierhout 1995) evaluating secondary care provider-led educational activities observed improvements. Vierhout and colleagues (Vierhout 1995) evaluated the effects of joint monthly consultant-general practitioner workshops for patients with orthopaedic problems. There were no significant differences detected 12 months following recruitment in the number of patients receiving laboratory tests, radiography, medication or physiotherapy referrals. They did observe an increase in general practitioners' use of injection therapy (30.6% study versus 11.7% control  $p < 0.001$ ), a reduction in subsequent referral to orthopaedic surgeons (35.4% study versus 68.0%  $p < 0.001$ ) and an increase in proportion of patients disorder free after one

year (35.4% study versus 23.7% control  $p < 0.05$ ).

Banait and colleagues (Banait 2000) evaluated the effects of consultant- led, general practice-based, small group educational workshops to disseminate guidelines for management of dyspepsia. They hypothesised that the intervention would increase appropriateness of referral for endoscopy, increase diagnostic yield of endoscopies, reduce expenditure on acid suppressing drugs and increase serological *Helicobacter Pylori* testing. Study practices had higher endoscopy referral rates, increased appropriateness of referral, marginally higher diagnostic yields, higher serology testing rates. However there was no reduction in prescriptions for acid suppressing drugs. Unfortunately there was a unit of analysis error and the statistical significance of these findings is unclear.

Grimshaw (Grimshaw 1998) evaluated small group general practitioner-consultant workshops for four tracer conditions. He observed a significant increase in the number of tracer referrals following the intervention against the hypothesised direction of effect.

Grimshaw (Grimshaw 1998) also found no significant improvements in referral following feedback on referral rates or discussion with an independent adviser.

### **Organisational interventions**

Bertakis and colleagues (Bertakis 1987) evaluated primary care provision for new patients in an Internal Medicine Clinic compared with a Family Practice Clinic. They observed fewer referrals and a lower annual per patient cost of laboratory tests for those patients seen in family practice. The difference in referral patterns was still noted whether the target of the referral was non-primary care, obstetrics-gynaecology, general surgery or dermatology.

There were fewer primary care attendances, fewer acute care visits and fewer emergency room visits for patients receiving primary care from family physicians. However, the authors report that the difference in emergency room visits may be due to access issues.

O’Cathain and colleagues (O’Cathain 1995) evaluated the effect of providing primary care based physiotherapy services. The aim of this service was to reduce orthopaedic referrals. They observed greater physiotherapy referrals, fewer orthopaedic referrals and fewer rheumatology referrals. Unfortunately, there was baseline imbalance for all of these outcomes which could undermine the post intervention differences. Furthermore, there was a unit of analysis error and the statistical significance of these findings is unclear.

Kinnersley and colleagues (Kinnersley 1999) evaluated the effects of an in-house second opinion before outpatient referral. They found that approximately 70% of patients having an in-house second opinion were judged to need referral to the same hospital discipline immediately (63.0%) or within 12 months (9.8%). Patients referred in-house were more likely to report themselves as satisfied with their care.

Bridgman et al (Bridgman 2005) evaluated the effect of a ‘slot system’ designed to reduce waiting times by allocating a predetermined number of consultations to an orthopedic specialist. There were relative reductions in the monthly referral rate per 10,000 population of 22% in the intervention group and 10% in the control group. No significance levels were reported, but the authors state that multifactorial linear regression demonstrated a significant reduction in referrals from the intervention group. However, the intervention group had a 14% lower referral rate at baseline and it is unclear whether

the analyses corrected for this. The imbalance raises concerns about the comparability of the intervention and control sites.

### **Financial interventions**

One study evaluated the effects of changing remuneration systems. Davidson and colleagues (Davidson 1992) evaluated the effects of a change in remuneration system from a low cost fee-for-service system to either a high cost fee-for-service system or capitation-based budgetary system. They observed a reduction in the number of non-primary care referrals by providers receiving capitation based remuneration but little effect in providers receiving increased fee-for-service.

Two studies evaluated the effects of the general practice fundholding scheme within the UK (Coulter 1993; Kammerling 1996). Coulter and colleague (Coulter 1993) compared referral rates from 10 'first wave' fundholding with 6 non-fundholding practices during the preparatory year (phase 1) and first year following the introduction of the scheme (phase 2). Referral rates during the preparatory year were used to set the budget for the first year. Referral rates were higher in fundholding practices during phase 1 but fundholding and non-fundholding practices had similar referral rates during phase 2. In the original report, the authors state that fundholders referral rates had significantly increased, however there was a unit of analysis error and re-analysis at practice level using T-tests did not detect a significant difference. There was a significant increase in non-fundholders referral rates from the pre to post intervention period (median pre intervention 95.9 annual referrals per 1000 population versus median post intervention 117.2 annual referrals per 1000

population, Mann Whitney test  $p < 0.01$ ). The authors also report referral rates for individual specialties. However, there was a unit of analysis error and insufficient data were presented to allow re-analysis of the data. Surender and colleagues (Surender 1995) published a follow up study presenting data for a third time period; however, by this time, four control practices had become fundholders or shadow-fundholders.

Kammerling and colleague (Kammerling 1996) evaluated the effects of fundholding on orthopaedic referral rates one and two years following referral in ten fundholding and twenty-two non-fundholding practices. There were reductions in the fundholding practices compared to controls but these were modest at best. There was a unit of analysis error and the statistical significance of these findings is unclear.

One study (Linnala 2001) evaluated the effect of providing access to private specialists or a hospital based specialist at the same cost to the patient. Normally, the cost for the private specialist was double or more the cost of the hospital based specialist. At baseline the rates of referral to a specialist were higher in the experimental group (5.7% age sex adjusted) than in the control group (4.4% age sex adjusted), increasing to 6.8% on the experimental group and 5.5% in the control group. The percentage of referrals sent to private specialist by the GPs in the control group increased from 5.7% to 33.6% in the experimental group but decreased slightly (8.8% to 5.6%) in the control group suggesting that there was a change in the destination rather than number of referrals.

## DISCUSSION

Despite the important role referral systems play in many health care systems, surprisingly few interventions have been rigorously evaluated. The majority of studies were conducted in the UK and the generalisability of these findings to other settings especially countries without a formal referral system is uncertain. As a result there is a limited evidence base to support policy decisions. Nevertheless it is possible to draw a number of preliminary conclusions. Passive dissemination of referral guidelines appears unlikely to lead to improvements in referral behaviour. This has implications for local or national referral guidelines; local dissemination and implementation activities appear necessary. The likely success of such local dissemination and implementation strategies appears to be increased if local secondary care providers are involved in educational activities.

Several studies observed improvements in the quality of referral when referral guidelines were disseminated with structured referral sheets which could be included in the referral letter. Structured referral sheets are checklists to be completed at the time of referral prompting the primary care physician about important elements of pre-referral investigation and management. In all three studies, the use of these structured referral sheets led to improved pre-referral investigation of patients ensuring that all appropriate examinations and investigations had been completed prior to referral. Whilst this is a potentially attractive intervention, general practices were only asked to use structured referral sheets for single conditions in each study and at best only about half of patients were referred with a completed sheet. There is a potential danger of overload if general

practitioners are requested to use referral sheets for a wider range of conditions. In the future, this might be addressed by advances in informatics (for example, on-line booking systems with embedded referral management sheets) but at present, these interventions should probably be used sparingly for referrals for common important conditions.

In the Thomas study (Thomas 2003), the guidelines and structured referral sheets were part of a complex intervention which included re-organisation of the secondary care system to streamline the referral process. The results of the study suggest that this was successful; patients were seen and had a management decision more rapidly. It is likely that this non-financial incentive was important for practitioners buy-in to the intervention.

In contrast, in the Morrison study (Morrison 2001) there was little evidence that secondary care management was influenced by the introduction of referral guidelines and that many investigations were unnecessarily repeated. The authors suggest that this might act as a disincentive to practitioners to comply with guidelines. Thus, it appears important that dissemination and implementation strategies for referral guidelines and similar interventions should consider the process of care across the primary - secondary care interface ensuring that secondary care providers make appropriate changes in the content and organisation of care to optimise the efficiency of the referral system.

Relatively few organisational interventions have been evaluated. Enhancement of primary care capacity (for example, providing general practice based physiotherapy services) may be useful although the effects of on-site mental health workers in primary care were uncertain (Bower 1999). One study evaluating the effects of in-house second opinions prior

to referral observed that approximately 30% of patients avoided subsequent referral. This is a potentially attractive intervention for primary care physicians working in group practices or multi-practice organisations (for example, independent practitioner associations in New Zealand, primary care groups or trusts within the UK) and should be explored further. In this update, one study with a slot system intervention was included; however it is unclear if this new system has any benefit and further research is required.

Four of the studies of financial interventions observed modest reductions in referral rates, although none of the studies attempted to evaluate quality of care. At this time there is insufficient evidence to draw firm conclusions about the potential effects of financial interventions. There is a danger that financial interventions may lead to an unselective reduction in referral, both rational and non-rational. A study allowing primary care physicians to refer patients to private specialist appeared to increase referrals to private specialists with little or no effect on overall referral rates.

The main weakness of the review is inevitably the limited number, methodological quality and limited evaluation of the identified studies. There have been relatively few evaluations of individual interventions, limiting ability to explore effect modifiers and confidence in the generalisability of the results to referrals for other conditions or in other settings. All of the studies had some methodological weaknesses, in particular, relatively few studies correctly analysed data from clustered randomised trials limiting statistical interpretation of the results. The studies demonstrate the complexity of undertaking research in this area.

Interventions to improve referral may influence general practice management of non-

referred patients, referral behaviour (number and quality of referrals), secondary care management of patients, the flow of patients through the referral system, patient outcomes and satisfaction, and resource use. No individual study managed to evaluate all these aspects. There is little evidence about the relationship between referral rates and appropriateness. As a result, it is difficult to interpret studies which only reported effects of interventions on referral rates. Only two studies undertook an economic evaluation despite the important impact of referral on resource use; furthermore the likely resources required for the different interventions would vary considerably.

For the update, we revisited the studies that were included in the original review for inclusion consideration, particularly the CBA designs. The decision was made by the EPOC review group not to include CBA studies with only one control and one intervention group. This resulted in one study (Krasnik 1990) being removed for the update.

Faulkner and colleagues (Faulkner 2003) undertook a broader review of primary-care based service innovations on the quality and patterns of referral to specialist secondary care. Some studies evaluated interventions that did not primarily aim to change outpatient referral rates or improve outpatient referrals appropriateness. Nevertheless their conclusions were broadly similar about the limitations of the current evidence base.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

Referral guidelines are more likely to be effective if local secondary care providers are

involved in dissemination activities, structured referral sheets are used, secondary care management is responsive to changes in primary care behaviour as a result of the guidelines and if they reflect local circumstances and address local barriers.

There are a limited number of rigorous evaluations to base policy on. Nevertheless, passive dissemination of referral guidelines is unlikely to lead to improvements in referral practice.

Referral guidelines are more likely to be effective if: local secondary care providers are involved in dissemination activities; structured referral sheets are used; secondary care management is responsive to changes in primary care behaviour as a result of the guidelines; and if they reflect local circumstances and address local barriers.

There is little evidence on the effects of organisational interventions but the use of 'in-house' second opinion and other intermediate primary care based alternatives to outpatient referral appear promising. Financial interventions can change referral rates but their effect on quality of referral is uncertain.

### **Implications for research**

Further research is needed to replicate the results of current evaluations (focusing on potentially effective interventions such as secondary care provider-led educational activities, structured referral management sheets, enhancement of primary care and in-house second opinions). Further research is also needed to explore a wide range of available interventions which do not appear to have been evaluated to date. In particular, it would be worth evaluating other intermediate primary-care based referral systems.

These evaluations should evaluate the effects of the intervention on the quantity and quality of referrals and include an economic evaluation.

## **POTENTIAL CONFLICT OF INTEREST**

JG is an author on several of the reviewed papers. RT is an author on one of the reviewed papers.

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Interventions to improve outpatient referrals from primary care to secondary care (Review)

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## Tables

### Characteristics of included studies

<b>Study</b>	<b>Abu-Ramadan 2002</b>
Methods	Design: ITS Completeness of data set: NOT CLEAR The intervention unlikely to affect data collection: DONE Sufficient data points to enable reliable statistical inference: DONE Formal test for trend: NOT CLEAR Blinded assessment : NOT DONE Reliable outcome measure(s): DONE The intervention is independent of other changes: DONE Type of data: CROSS SECTIONAL
Participants	PALESTINE 40 Physicians (GPs) in the Gaza Strip
Interventions	(1) Educational Meetings (2) New Referral and Reply Sheet (3) New Staff (4) Change in Equipment and Facilities (5) Quality Monitoring Mechanisms
Outcomes	Patient Load
Notes	EDUCATIONAL INTERVENTION ORGANISATIONAL INTERVENTION
Allocation concealment	D – Not used
<b>Study</b>	<b>Banait 2000</b>
Methods	Design: RCT (Practice randomised 2 arm trial) Randomisation concealment: DONE (but see note) Follow up: Providers: DONE Patients: NOT CLEAR Blinded assessment: DONE/NOT CLEAR Baseline: DONE/NOT CLEAR Reliable outcomes: DONE/NOT CLEAR Protection against contamination: DONE
Participants	UK General practitioners in 114 general practices in Salford and Trafford Health Authority.

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	Proportion of eligible providers who participated: 99.1% (114/115 practices) 33/57 (58%) of intervention practices received the intervention. Clinical area of interest: dyspepsia
Interventions	(1) Consultant led educational seminars plus paper copies of guidelines. Reinforcement practice visit at 3 months. (2) Paper copies of guidelines
Outcomes	Process: Appropriateness of referral for upper gastrointestinal endoscopy Findings at endoscopy Prescribing costs for acid suppressing drugs Requests for laboratory tests for Helicobacter Pylori
Notes	EDUCATIONAL INTERVENTION Allocation used minimisation based on practice size, fundholding status, previous expenditure on NSAIDs and previous involvement in a guideline initiative.
Allocation concealment	A – Adequate
<b>Study</b>	<b>Bennett 2001</b>
Methods	Design: RCT (cluster randomized by practice) Protection against contamination: DONE Blinded assessment: DONE Reliable outcome measure(s): DONE Baseline measurement: DONE Follow-up: NOT DONE
Participants	UK 177 Physicians (GPs) in 50 practices
Interventions	(1) Risk Factor Checklist (2) OME Training Video (3) Combination of Checklist and Video
Outcomes	Appropriateness of Referrals
Notes	EDUCATIONAL INTERVENTION
Allocation concealment	D – Not used
<b>Study</b>	<b>Bertakis 1987</b>
Methods	Design: RCT (Patient randomised two arm trial) Randomisation concealment: NOT CLEAR Follow up: Providers: NOT CLEAR Patients: DONE Blinded assessment: NOT CLEAR Baseline: NOT CLEAR Reliable outcomes: NOT CLEAR

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	Protection against contamination: DONE
Participants	US 520 patients attending US Medical Center Clinical area of interest: general management of problem
Interventions	(1) Primary care management in family practice clinic (2) Primary care management in internal medicine clinic
Outcomes	Process: Primary care consultations Emergency room and acute care clinic attendance's Specialist clinic attendances Costs of laboratory tests
Notes	ORGANISATIONAL INTERVENTION
Allocation concealment	B – Unclear

<b>Study</b>	<b>Bridgman 2005</b>
Methods	Design: CBA Baseline measurements: NOT DONE Characteristics of second site: NOT DONE Follow up: Providers: NOT CLEAR Patients: N/A Blinded assessment: DONE Reliable outcome measures: DONE Protection against contamination: DONE
Participants	UK 36 practices; 12 intervention, 24 control
Interventions	Slot system, providing a limited number of spots for new orthopedic referrals
Outcomes	Process: Rate of new referrals to orthopedics
Notes	ORGANISATIONAL INTERVENTION
Allocation concealment	D – Not used

<b>Study</b>	<b>Coulter 1993</b>
Methods	Design: CBA Baseline measurements: NOT DONE Characteristics of second site: NOT CLEAR Follow up: Providers: NOT CLEAR Patients: N/A Blinded assessment: NOT DONE <sup>a</sup> Reliable outcome measures: NOT CLEAR (see note) Protection against contamination: DONE
Participants	UK Ten fundholding (study) and six non-fundholding (control) practices in Oxford

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	region. During latter part of study four control practices were in preparation for fund holding. Proportion of participating practices: 40% (10/25) fundholding practices.
Interventions	(1) Fundholding scheme. (2) No intervention (during latter stage of the study, four control practices were in preparation for fundholding).
Outcomes	Process: Number of outpatient referrals that would incur a charge against fundholders' budgets.
Notes	PROFESSIONAL FINANCIAL INTERVENTION Data were collected by general practitioner or practice staff.
Allocation concealment	D – Not used

<b>Study</b>	<b>Davidson 1992</b>
Methods	Design: RCT (2 arm physician randomised trial) Randomisation concealment NOT CLEAR Follow up Provider NOT CLEAR Patients NOT CLEAR Blinded assessment NOT CLEAR Baseline NOT CLEAR Reliable outcomes NOT CLEAR Protection against contamination NOT CLEAR Method of randomisation not clear Unit of analysis error
Participants	US 80 physicians in private office based practices who treated Medicaid children and more than \$2000 in Medicaid billings in previous year. Medicaid eligible children receiving welfare benefit under Aid for Families with Dependent Children Program Proportion of eligible practitioners who participated: 57.1% (80/140).
Interventions	(1) Capitation (I1) (2) Fee for service (high rate) (I2) (3) Control - fee for service low rates (see note)
Outcomes	Process: Mean number of primary care visits Mean number of non primary care visits Mean number of clinic/emergency department visits Mean number of hospitalisations
Notes	PROFESSIONAL FINANCIAL INTERVENTION Comparison group drawn from community based sample of patients who were recertified for Aid for Families programme in the month before or after study

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	recruitment.
Allocation concealment	B – Unclear
<b>Study</b>	<b>Emslie 1993</b>
Methods	Design: RCT (Practice randomised 2 arm trial) Randomisation concealment: NOT CLEAR Follow up: Providers: NOT CLEAR Patients: DONE Blinded assessment: NOT DONE Baseline: NOT CLEAR Reliable outcomes: NOT CLEAR Protection against contamination: DONE
Participants	UK General practitioners in 82 general practices in Grampian region of Scotland. Proportion of eligible practices who participated: 95.3% (82/86 practices participated but nine individual general practitioners from participating practices declined to take part in study). Clinical area of interest: infertility
Interventions	1) Locally developed guidelines plus structured record sheet (incorporating reminders) for general practice management and referral of infertile couples disseminated by mail. (2) No intervention (control GPs were informed that they would receive the guidelines at the end of the study).
Outcomes	Process: Compliance with guidelines in particular whether adequate sexual history was taken, whether couple were appropriately examined and investigated (see note).
Notes	EDUCATIONAL INTERVENTION Differences in data collection methods between study and control GPs.
Allocation concealment	B – Unclear
<b>Study</b>	<b>Grimshaw 1998</b>
Methods	Design: CCT (Practice allocated 4x4 Latin square with embedded factorial design) Randomisation concealment: NOT CLEAR Follow up: Providers: DONE Patients: DONE Blinded assessment: NOT DONE Baseline: DONE Reliable outcomes: NOT CLEAR Protection against contamination: DONE
Participants	UK

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	116 general practitioners from the Grampian region. Proportion of eligible providers who participated: 38.8% (116/299). Clinical areas of interest: low back pain, menorrhagia, suspected peptic ulcer, varicose veins
Interventions	(1) Locally developed referral guidelines disseminated by mail. (2) Consultant-general practitioner workshops (3) Feedback on referral rates (4) Discussion about referrals with an independent adviser Interactions between 1 + 2 and 3 + 4 also tested for. (5) No intervention
Outcomes	Process: Total number of referrals Number of referrals for tracer conditions Appropriateness of referral Use of specialised hospital investigations Use of specialised hospital treatments
Notes	EDUCATIONAL INTERVENTION
Allocation concealment	B – Unclear

<b>Study</b>	<b>Jones 1993</b>
Methods	Design: RCT (Practice randomised 2 arm trial) Randomisation concealment: DONE Follow up: Providers: DONE Patients: N/A Blinded assessment: NOT CLEAR Baseline: NOT CLEAR Reliable outcomes: DONE/NOT CLEAR Protection against contamination: DONE
Participants	UK 179 general practitioners from 45 general practices. Proportion of eligible providers who participated: 70% (179/254). Clinical area of interest: dyspepsia
Interventions	(1) Local consensus meetings between general practitioners, surgeons, physicians and radiologists to agree guidelines for management of dyspepsia including choice and timing of investigations, when to refer for specialist advice and management. Guidelines distributed to study general practices. (2) No intervention.
Outcomes	Process: Medical and surgical referrals for upper gastrointestinal symptoms. Referrals for endoscopy. Referrals for upper gastrointestinal radiology investigations. Prescriptions of upper gastrointestinal drugs.

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	Prescriptions of ulcer healing drugs.
Notes	EDUCATIONAL INTERVENTION
Allocation concealment	A – Adequate
<b>Study</b>	<b>Kammerling 1996</b>
Methods	Design: CBA Baseline measurements: DONE Characteristics of second site: DONE Follow up: Providers: NOT CLEAR Patients: N/A Blinded assessment: DONE Reliable outcome measures: DONE Protection against contamination: DONE
Participants	UK 10 fundholding (study) and 22 non fundholding (control) practices Proportion of participating practices: not clear
Interventions	(1) Fundholding scheme. (2) No intervention
Outcomes	Process: Referral rates for orthopaedic problems.
Notes	PROFESSIONAL FINANCIAL INTERVENTION
Allocation concealment	D – Not used
<b>Study</b>	<b>Kinnersley 1999</b>
Methods	Design: RCT (Practice randomised 2 arm RCT) Randomisation concealment: NOT CLEAR Follow up: Providers: NOT CLEAR Patients: NOT DONE Blinded assessment: NOT CLEAR Baseline: NOT DONE Reliable outcomes: DONE Protection against contamination: DONE
Participants	UK General practitioners from 15 practices in East Cardiff and Gwent (see note a). Proportion of eligible practices who participated: Not clear Clinical area of interest: outpatient referrals for dermatological, gynaecological, ophthalmological, ENT and musculo-skeletal problems
Interventions	1) Patients referred for an 'in house' second opinion prior to referral (2) No intervention
Outcomes	Process:

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	<p>Number of referrals to hospital (Study group only)          Number of referrals immediately and within 6 months of in-house referral          Outcome:          Medical Interview          Satisfaction Scale          SF-36 health status measure          Both measured at baseline, 6 months and 12 months (see note b).</p>
Notes	<p>ORGANISATIONAL INTERVENTION          a. 16 practices were recruited but 1 withdrew following allocation to control arm.          b. Baseline outcome questionnaires were administered after in house referral (study group) and after consultation when referral was made (control group).</p>
Allocation concealment	B – Unclear
<b>Study</b>	<b>Linnala 2001</b>
Methods	<p>Design: CBA          Baseline measurement: DONE          Blinded assessment : DONE          Reliable outcome measure(s): DONE          Follow-up: NOT CLEAR</p>
Participants	<p>FINLAND          14 Physicians (GPs) in 4 municipal health centers</p>
Interventions	<p>(1) Patient Incentives          (2) Provided GPs with list system for referrals</p>
Outcomes	<p>Rate of Referrals to Public vs Private Sectors          Referrals: Consult vs Care</p>
Notes	<p>FINANCIAL INTERVENTION          ORGANISATIONAL INTERVENTION</p>
Allocation concealment	D – Not used
<b>Study</b>	<b>Morrison 2001</b>
Methods	<p>Design: RCT (practice randomised)          Blinded assessment : DONE          Reliable outcome measure(s): NOT CLEAR          Baseline measurement: NOT DONE          Follow-up: DONE</p>
Participants	<p>UK          598 Physicians (GPs) in 214 practices in Glasgow</p>
Interventions	<p>(1) Distribution of Locally Developed Guidelines          (2) Structured record sheet checklist for GPs incorporating reminders          (3) Educational Meetings</p>
Outcomes	<p>Rate of Referrals          Appropriate pre-referral investigations</p>

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

	Hospital investigations after referral Time to management decision Cost of referrals to NHS
Notes	EDUCATIONAL INTERVENTION
Allocation concealment	A – Adequate
<b>Study</b>	<b>O’Cathain 1995</b>
Methods	Design: CBA Baseline measurements: NOT DONE/NOT CLEAR Characteristics of second site: NOT CLEAR Follow up: Providers: NOT CLEAR Patients: NOT CLEAR Blinded assessment: DONE Reliable outcome measures: DONE Protection against contamination: DONE
Participants	UK 41 non fund-holding general practices in Doncaster. Proportion of eligible practices who participated: Not clear Clinical area of interest: musculoskeletal conditions
Interventions	1) Access to a primary care based physiotherapy service (2) No intervention (GPs had access to a hospital based physiotherapy service)
Outcomes	Process: Physiotherapy contact rates Orthopaedic referral rate Rheumatology referral rate
Notes	ORGANISATIONAL INTERVENTION
Allocation concealment	D – Not used
Methods	Design: RCT (Practice randomised 2 x 2 balanced incomplete block design) Randomisation concealment: DONE Follow up: Providers: DONE (see note) Patients: DONE Blinded assessment: NOT CLEAR Baseline: DONE Reliable outcomes: NOT CLEAR Protection against contamination: DONE
Participants	UK General practitioners in 76 general practices in the Grampian Region.A Proportion of eligible practices who participated: 84.4% Clinical area of interest: prostatism, microscopic haematuria

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

Interventions	(1) Locally developed referral guidelines, disseminated by educational meetings. General practitioners could refer patients to a fast track day case investigation service if they used a structured referral letter based on guidelines. (2) No intervention
Outcomes	Process: Proportion of patients referred through fast track system Number of referrals Case mix of referrals <i>Compliance with referral guidelines</i> General practitioner pre and post referral workload Waiting time from referral until first appointment Management decision reached after one hospital appointment Completed care within 12 months Waiting time for all urology referrals Outcomes: SF36 and condition specific measures at baseline and 12 months Economic evaluation
Notes	EDUCATIONAL INTERVENTION Data from 10 practices were excluded from analysis due to incomplete data capture that could lead to an overestimate of the effects of the intervention.
Allocation concealment	A – Adequate

<b>Study</b>	<b>Vierhout 1995</b>
Methods	Design: RCT (Patient randomised 2 arm trial - Zelen design) Randomisation concealment: NOT CLEAR Follow up: Providers: N/A Patients: DONE Blinded assessment: NOT CLEAR Baseline: NOT DONE Reliable outcomes: NOT CLEAR Protection against contamination: NOT DONE
Participants	Netherlands 272 patients with orthopaedic problems cared for by 12 Dutch general practitioners. Patient was selected if GP was uncertain about diagnosis or management and <i>specialist referral was considered</i> . Proportion of eligible providers who participated: not specified. Clinical area of interest: patients considered for orthopaedic referral
Interventions	(1) General practitioners and consultants operated a joint consultation session for patients with orthopaedic problems where the general practitioner was uncertain about diagnosis and management and referral was considered. (2) Routine general practitioner care.

Interventions to improve outpatient referrals from primary care to secondary care (Review)

Characteristics of included studies (*Continued*)

Outcomes	Process (GP actions): Diagnostic actions. Therapeutic measures. Referrals to orthopaedic surgeon. Outcome: General health status (based on Netherlands Central Statistics Bureau Questionnaire). Level of industrial disability. Activities of daily living.
Notes	EDUCATIONAL INTERVENTION
Allocation concealment	B – Unclear

## Characteristics of excluded studies

<b>Study</b>	<b>Reason for exclusion</b>
Harris 2002	Contamination of control group Ceiling effect Only 11% follow-up of professionals
Jaatinen 2002	Outcome not objectively measured: questionnaires, self-report
Krasnik 1990	Only one intervention and one control group
Rosenheck 2000	Ineligible outcomes
Schulpen 2003	Insufficient baseline data
Wilson 2005	Ineligible outcomes

ADDITIONAL TABLES

Table 01. Summary of Results

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
Abu-Ramadan 2002	Monthly observations for: 19 months before intervention 29 months following intervention		Patient Load on Eye Hospital Staff Pre Intervention: M =5961.89/month Post Intervention: M =3866.38/month Absolute Difference (M): 2095.51 patients per month	Not assessed	EDUCATIONAL INTERVENTION ORGANISATIONAL INTERVENTION Multifaceted intervention was independent of other changes, but any effect of referrals component specifically is impossible to separate from other elements of the intervention. Other outcomes of interest were listed and measured, but only patient load results were actually reported in the article.
Banait 2000	6 - 7 months following intervention		Referral rates (referrals per 10,000 patients) Post intervention: 1.42 (study) vs 0.92 (control) a Absolute difference (post): 0.50 referral per 10,000 patients Relative % difference (post): +54%b Appropriateness of upper gastrointestinal endoscopy: Post intervention: 62.5% (study) vs 50.8% (control) (p =*)a Absolute difference: +11.7% (study better) Relative difference: +23.0% Findings at endoscopy Normal: Pre intervention 37.8% (study) vs 39.1% (control) Post intervention 39.5% (study) vs 43.4% (control) (p =*)a Absolute difference		EDUCATIONAL INTERVENTION only 68% of practices included in complete study (a) Unit of analysis error (b) Hypothesised direction unclear

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>post: - 3.9% (study better)                      Relative difference                      post: -9.0%                      Absolute difference from baseline: 1.7% (study) vs 4.3% (control)                      Difference in absolute change from baseline: -2.6%                      Prescribing costs for acid suppressing drugs                      Overall expenditure (net ingredient cost per prescribing unit):                      Pre intervention: 4.10 (study) vs 4.08 (control)                      Post intervention: 4.43 (study) vs 4.16 (p =*)a                      Absolute difference post: + 0.27 (study worse)                      Relative post difference: + 6.5%                      Absolute difference from baseline: 0.33 (study) vs 0.08 (control)                      Difference in absolute change from baseline: + 0.25 Requests for laboratory tests for Helicobacter Pylori                      Post intervention (median per practice): 4 (study) vs 0 (control) (p&lt; 0.001 Mann- Whitney test) (study better)</p>		
Bennett 2001	One year following intervention	Control (no intervention) vs Checklist vs Video vs Checklist and Video	PPV (%) - Appropriateness of Referrals Pre Intervention Means Checklist Group:	EDUCATIONAL INTERVENTION only 68% of practices included in complete study	

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			35.57% Video Group: 42.37% Checklist & Video Group: 23.49% Control Group: 45.75% Post Intervention Means Checklist Group: 15.97% Video Group: 23.97% Checklist & Video Group: 51.59% Control Group: 15.15% Pre-post change (M) Checklist Group: -19.6% [95% CI (-44.8, 5.6)] Video Group: -18.4% [95% CI (-35.2, -1.6)] Checklist & Video Group: +28.1% (ANOVA P=0.002) [95% CI (10.2, 46.0)] Control Group: -30.6% [95% CI (-69.9, 8.66)]		
Bertakis 1987	Mean length of follow up 2.1 years	Family medicine vs internal medicine	Number of primary care attendances per year: Post intervention 2.6 (family medicine FM) vs 3.2 (internal medicine IM) p<0.001 Absolute difference post: -0.6 attendances Relative percentage difference: -18.8% Proportion of patients with no emergency room attendances Post intervention: 67.5% (FM) vs 55.2% (IM) ( p <0.01)a	Not assessed	ORGANISATIONAL INTERVENTION (a) Based on re analysis of 2 x 2 Chi square no visit vs any visit using Arcus Biostat.

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Absolute difference (post): +15.3%</p> <p>Relative percentage difference: +22.7%</p> <p>Proportion of patients with no acute care clinic visits</p> <p>Post intervention: 64.6%</p> <p>(FM) vs 57.0% (IM) (p =NS)<sup>a</sup></p> <p>Absolute difference (post): +7.6%</p> <p>Relative percentage difference: +11.8%</p> <p>Proportion of patients with no non primary care clinic attendances</p> <p>Post intervention: 56.1% (FM) vs 38.6% (IM) (p &lt;0.001)<sup>a</sup></p> <p>Absolute difference (post): +17.5%</p> <p>Relative percentage difference: +31.2%</p> <p>(Significantly fewer reductions to obstetrics and gynaecology, general surgery and dermatology clinic noted in family practice group)</p> <p>Median annual costs per patient of laboratory tests</p> <p>Post intervention: \$64 (FM) vs \$93 (IM) (p &lt; 0.01 Wilcoxon rank sum test)</p> <p>Absolute difference (post): -\$29</p> <p>Relative percentage difference: -31.3%</p>		
Bridgman 2005	18 months	New slot system vs control	Rate of referrals/ 10,000patients/month Baseline Intervention	Not assessed	ORGANISATIONAL INTERVENTION

Interventions to improve outpatient referrals from primary care to secondary care (Review)

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			9.40 (SE 0.41) Baseline Control 10.99 (SE 0.52) 12 months Intervention 7.29 (SE 0.31) Relative improvement 22% 12 months Control 9.90 (SE 0.39) Relative improvement 10% 18 months Intervention 7.31 (SE 0.0.21) Relative improvement 22% 18 months Control 11.70 (SE 0.48) Relative improvement -6%		
Coulter 1993	6 months pre- intervention (-6 - 0 months) and 6 (7 - 12 months) post- intervention.	Fundholding vs control.	Standardised mean annual referral rates per 1000 population per year NHS Pre intervention: 109.7 (study) vs 97.5 (control) Post intervention: 112.1 (study) vs 122.3 (control) (NS) <sup>a</sup> Absolute difference (post): -10.3 Relative percentage difference (post): -8.4% Absolute difference from baseline: +2.1 (study) vs + 24.8 (control) Difference in absolute change from baseline: -22.7 Private Pre intervention: 29.4 (study) vs 27.7 (control)	Not assessed.	PROFESSIONAL FINANCIAL INCENTIVES (a) Unit of analysis error. Reanalysed using T-tests in Arcus Biostat.

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			Post intervention:26.6 (study) vs 28.8 (control) (NS)a Absolute difference (post): -2.2 Relative percentage difference (post): -7.6% Absolute difference from baseline: -2.8 (study) vs +1.1 (control) Difference in absolute change from baseline: -4.5		
Davidson 1992	6 months pre intervention, post intervention time period not specified	Capitation (I1) vs high fee for service (I2) vs low fee for service (control)	Mean annual number of primary care visits Pre intervention: 3.22 (I1) vs 3.68 (I2) vs 3.06 (control) Post intervention: 2.89 (I1) vs 3.71 (I2) vs 2.47(control)a Absolute difference (post): I1 vs control +0.42 I2 vs control +1.24 I1 vs I2 - 0.82 Relative percentage difference: I1 vs control +17.0% I2 vs control +50.2% I1 vs I2 -22.1% (relative to I2) Absolute difference from baseline: -0.33 (I1) vs +0.03 (I2) vs -0.59 (control) Difference in absolute change from baseline: I1 vs control +0.26 I2 vs control +0.62 I1 vs I2 -0.36	Not assessed	PROFESSIONAL FINANCIAL INCENTIVES Unit of analysis error

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			Mean annual number of non primary care visits Pre intervention: 0.62 (I1) vs 0.67 (I2) vs 0.61 (control) Post intervention: 0.57 (I1) vs 0.85 (I2) vs 0.80 (control) Absolute difference (post): I1 vs control -0.23 I2 vs control +0.05 I1 vs I2 -0.28 Relative percentage difference: I1 vs control -28.8% I2 vs control +6.25% I1 vs I2 -32.9% (relative to I2) Absolute difference from baseline: -0.042 (I1) vs -0.070 (I2) vs -0.031 (control) Difference in absolute change from baseline: I1 vs control -0.011 I2 vs control -0.039 I1 vs I2 +0.028		
Emslie 1993	Post intervention measurement only - during 9 months following intervention	Guidelines plus structured management/ referral sheet	Sexual history Knowledge of fertile period: Post intervention: 85% (Study) vs 73% (Control) (p = *)a Absolute difference (post): +12% (study better) Relative % difference (post): +15.7% Use of fertile period: Post intervention: 85% (Study) vs 69%	Not assessed	EDUCATIONAL INTERVENTION Unit of analysis error

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			(Control) (p = *)a Absolute difference (post): +16% (study better) Relative % difference (post): +23.2% Erectile problems: Post intervention: 86% (Study) vs 70%		
			(Control) (p = *)a Absolute difference (post): +16% (study better) Relative % difference (post): +22.9% Ejaculatory problems: Post intervention: 86%(Study) vs 70%		
			(Control) (p = *)a Absolute difference (post): +16% (study better) Relative % difference (post): +22.9% Dyspareunia: Post intervention: 86% (Study) vs 80%		
			(Control) (p = *)a Absolute difference (post): +6% (study better) Relative % difference (post): +7.5% Pre referral examination and investigations – female partner General examination: Post intervention: 68% (Study) vs 52%		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>(Control) (p = *)a            Absolute difference (post): +16% (study better)            Relative % difference (post): 30.8%            Pelvic examination: Post intervention: 67% (Study) vs 51% (Control) (p = *)a            Absolute difference (post): +16% (study better)            Relative % difference (post): +31.4%            Full blood count: Post intervention: 37% (Study) vs 13% (Control) (p= *)a            Absolute difference (post): +24% (study better)            Relative % difference (post): +184.6%            Progesterone: Post intervention: 72% (Study) vs 41% (Control) (p = *)a            Absolute difference (post): +31% (study better)            Relative % difference (post): +75.6%            Rubella status: Post intervention: 64% (Study) vs 25% (Control) (p = *)a            Absolute difference (post): +39% (study better)            Relative % difference (post): +156%            Pre referral examination and</p>		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>investigations - male partner                      Seen by general practitioner:                      Post intervention: 50% (Study) vs 33% (Control) (p = *)a                      Absolute difference (post): +17% (study better) Relative % difference (post): +51.5%                      Genital examination: Post intervention: 39% (Study) vs 13% (Control) (p = *)a                      Absolute difference (post): +26% (study better) Relative % difference (post): +200%                      Semen analysis: Post intervention: 51% (Study) vs 41% (Control) (p= *)a                      Absolute difference (post): +10% (study better) Relative % difference (post): +24.4%</p>		
Grimshaw 1998	4 months pre and 4 months post intervention	(1) Dissemination of guidelines. (2) GP-consultant small group discussions (3) Feedback of referral rates (4) Discussion with independent medical adviser	<p>Total number of referrals                      No significant changes detected with any intervention.                      Number of tracer referrals                      No significant changes detected with interventions                      1, 3, 4.                      Intervention 2 - mean number of referrals                      (b) Pre intervention: 1.67 (Study) vs 1.36 (Control)</p>	Not assessed	EDUCATIONAL INTERVENTION (a) Due to design it is not possible to present data simply. (b) Data analysed using general linear modelling.

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Post intervention: 1.62 (Study) vs 1.04 (Control) (p= 0.04)<sup>b</sup> Absolute difference (post): +0.58 referrals (study worse) Relative difference (post): +55.7% Absolute change from baseline: - 0.05 (Study) vs -0.32 (Control) Difference in absolute change from baseline: -0.27(study worse) Appropriateness of referral No significant changes detected with any intervention. Use of specialised hospital investigations No significant changes detected with any intervention. Use of specialised hospital treatments No significant changes detected with any intervention.</p>		
Jones 1993	6 months pre and 6 months post intervention.	Consensus guidelines vs no intervention.	<p>Medical and surgical referrals for upper gastrointestinal problems per GP: Pre intervention: 4.5 (Study) vs 3.92 (Control) Post intervention: 3.95 (Study) vs 2.85 (Control) (p= *)<sup>a</sup> Absolute difference (post): +1 referral <sup>b</sup> Relative % difference (post): -35.1% Absolute change from baseline: -0.55 (Study) vs - 1.07 (Control)</p>	Not assessed	<p>EDUCATIONAL INTERVENTION (a) Unit of analysis error (p values not reported) (b) Hypothesised direction unclear (c) Within group analyses reported in paper; post intervention across group analysis recalculated from summary statistics using Arcus Biostat.</p>

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Difference in absolute change from baseline: +0.52</p> <p>Referrals for endoscopy per GP: Pre intervention: 1.54 (Study) vs 1.32 (Control)</p> <p>Post intervention: 1.86 (Study) vs 1.42 (Control) (p= *)<sup>a</sup></p> <p>Absolute difference (post): +0.44 referral (study better)</p> <p>Relative % difference (post): +31.0%</p> <p>Absolute change from baseline: +0.32 (Study) vs +0.1 (Control)</p> <p>Difference in absolute change from baseline: +0.22</p> <p>Referrals for upper gastrointestinal radiology investigations: Pre intervention: 3.59 (Study) vs 3.07 (Control)</p> <p>Post intervention: 2.99 (Study) vs 2.71 (Control) (p= *)<sup>a</sup></p> <p>Absolute difference (post): +0.21 referrals (study worse)</p> <p>Relative % difference (post): +7.7%</p> <p>Absolute change from baseline: -0.6 (Study) vs -0.36 (Control)</p> <p>Difference in absolute change from baseline: -0.24 referrals (study better) Mean prescription costs of upper gastrointestinal drugs per GP (£): Pre</p>		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			intervention: £2634 (Study) vs £2254 (Control) Post intervention: £3215 (Study) vs £2545 (Control) (p<0.01)c Absolute difference (post): +£670b Relative % difference (post): +26.4% Absolute change from baseline: +£581 (Study) vs +£291 (Control) Difference in absolute change from baseline: +£290 Mean prescription costs of ulcer healing drugs per GP (£): Pre intervention: £1614 (Study) vs £1504 (Control) Post intervention: £2124 (Study) vs £1703 (Control) (p<0.01)c Absolute difference (post): +£421b Relative % difference (post): +24.7% Absolute change from baseline: +£510 (Study) vs +£199 (Control) Difference in absolute change from baseline: +£311		
Kammerling 1996	1 year pre and 1 year (T1) and 2 years (T2) post intervention	Fundholding vs control	Orthopaedic referral rates per 1000 population per year T1 Pre intervention: 7.96 (study) vs 8.23 (control)a	Not assessed	PROFESSIONAL FINANCIAL INCENTIVES (a) Referral rates calculated from data presented using total populations covered. (b) Unit of analysis error.

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Post intervention: 9.21 (study) vs 9.79 (control)<sup>b</sup> Absolute difference (post): -0.58 Relative percentage difference (post): -5.9% Absolute difference from baseline: +1.25 (study) vs +1.56 (control) Difference in absolute change from baseline: -0.31 T2 Pre intervention: 7.96 (study) vs 8.23 (control)<sup>a</sup> Post intervention: 9.00 (study) vs 10.97 (control)<sup>b</sup> Absolute difference (post): -1.97 Relative percentage difference (post): -18.0% Absolute difference from baseline: (study) +1.04 vs +2.74 (control) Difference in absolute change from baseline: -1.70</p>		
Kinnersley 1999	Timescale not clear	In house referral vs control	<p>Number of referrals 177 (study – 8 practices) vs 145 (control - 7 practices) Outcomes of in-house referrals Study practices only – 109 (63.0%) judged in need of immediate referral; 13 (7.5%) referred to same hospital speciality as</p>	<p>Patient satisfaction and SF36 scores: Data not presented in format allowing data abstraction. Authors report that patients</p>	ORGANISATIONAL INTERVENTION

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			their in-house referral within 12 months; 17 (9.8%) referred to other hospital speciality within 12 months; 34 (19.6%) not referred within 12 months (missing data on 4 patients). Patients referred immediately were more likely to be older and have worse SF36 physical function score.	referred in house were more likely to report themselves as satisfied compared to patients referred directly to hospital.	
Linnala 2001	33 months following intervention	Control (no intervention) vs Patient incentives and Referrals list system	Referral Rate Pre Intervention G1 M = 4.4% p < 0.05 G2 M = 5.7% p < 0.05 Post Intervention G1 M = 5.5% p < 0.001 G2 M = 6.8% p < 0.001 Percentage relative change 1.1% p < 0.001 Referrals Sent to Private Services Pre Intervention G1 M = 8.8% G2 M = 5.7% Post Intervention G1 M = 5.6% p < 0.001 G2 M = 33.6% p < 0.001 Percentage relative change G1 - 3.2%G2 27.9%	Not assessed	FINANCIAL INTERVENTION ORGANISATIONAL INTERVENTION
Morrison 1999	12 months post intervention		Referral rate per 1000 women aged 20 to 44 Post intervention: 3.25 (Study) vs 3.27 (Control) (p= *)a Absolute difference (post): -0.02 referrals (b) Relative % difference (post):-0.6% Pre referral management	Pregnancy rates with 12 months of referral Post intervention: 32.1% (Study) vs (control) (p=*)a,c Absolute	EDUCATIONAL INTERVENTION (a) Unit of analysis error. (b) Hypothesised direction unclear (c) Derived from multilevel model after correction for deprivation and referral hospital. (d) Further information sought from author

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Proportion of couples receiving all appropriate investigations/advice</p> <p>Post intervention: 16.5% (Study) vs 6.9% (Control) (OR 1.324, 95%CI 1.001 to 1.752, p =0.025)c</p> <p>Absolute difference (post): +9.6% (study better)</p> <p>Relative % difference (post): +139.1%</p> <p>Progesterone:</p> <p>Post intervention: 56.2% (Study) vs 48.4% (Control) (OR 1.464, 95%CI 0.927 to 2.312, p=0.051)c</p> <p>Absolute difference (post): +7.8% (study better)</p> <p>Relative % difference (post): +16.1%</p> <p>Semen analysis:</p> <p>Post intervention: 37.3% (Study) vs 30.6% (Control) (OR 1.337, 95% CI 0.837to 2.134, p = 0.112)c</p> <p>Absolute difference (post): +6.7% (study better)</p> <p>Relative % difference (post): +21.9%</p> <p>Cervical smear checked within previous 3 years:</p> <p>Post intervention: 85.9% (Study) vs 85.5% (Control) (OR 1.052, 95% CI 0.533 to 2.002 p = 0.438)c</p>	<p>difference (post): -8.2%</p> <p>Relative percentage difference: -25.5%</p>	

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Absolute difference (post): +0.04% (study better) Relative % difference (post): +0.47% Advice given about folic acid: Post intervention: 57.0% (Study) vs 49.7% (Control) (OR 1.313, 95% CI 0.852 - 2.023, p = 0.109)<sup>c</sup> Absolute difference (post): +7.3% (study better) Relative % difference (post): +14.7% Rubella immunity status checked: Post intervention: 44.6% (Study) vs 36.2% (Control) (OR 1.415, 95% CI 0.930 to 2.153, p = 0.052)<sup>c</sup> Absolute difference (post): +8.4% (study better) Relative % difference (post): +23.2% Post referral general practice management No significant difference in the number of consultations about infertility in the 12 months following referral (b) Hospital management Time from first appointment to management plan: Post intervention: 3.34 months (study) vs 2.98 months</p>		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>(control)(p = 0.24)d            Absolute difference            (post) = -0.36 months            Relative % difference            (post) = -12.1%            Mean number of            appointments before            management plan            reached:            Post intervention:            1.92 (study) vs 1.91            (control) (p=0.84)d            Absolute difference            (post) = -0.01            appointment            Relative % difference            (post) = -0.005%            Proportion of couples            with management            plan at one year            Post intervention:            50.9% (study) vs            44.3% (control)            (Odds ratio 1.24, 95%            CI 0.87 to 1.77,            p-value = 0.24)            Absolute difference            (post): +6.6%            Relative % difference            (post): +14.9%            Economic evaluation            GP costs:            Post intervention: £23            (study) vs £15            (control) (p =*) a, d            Absolute difference            (post): +£8 (study            more expensive)            Relative % difference            (post): +53.3%            Hospital costs            Post intervention:            £214 (study) vs £196            (control) (p = *)a,d            Absolute difference            (post): +£18 (study            more expensive)            Relative % difference</p>		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
O’Cathain 1995	12 months pre (4/91 - 3/92) and 12 month post (4/92 -3/93) <sup>a</sup> 9 month pre and 9 month post intervention (orthopaedic and rheumatology referrals)	General practice based physiotherapy service vs control	<p>(post): +9.2% Total NHS costs Post intervention: £251 (study) vs £215 (control) (p = *)<sup>a,d</sup> Absolute difference (post): +£36 Relative % difference (post): +16.7%</p> <hr/> <p>Physiotherapy contact rate (per 1000 practice population)<sup>b</sup> Pre intervention: 11.7 (study) vs 6.6 (control) Post intervention: 21.0 (study) vs 7.4 (control) Absolute difference (post): + 13.6 contacts per 1000 practice population Relative percentage difference: +183.8% Absolute difference from baseline: +9.3 contacts per 1000 practice population (study) vs + 0.8 (control) Difference in absolute change from baseline: +8.5 contacts per 1000 practice population Orthopaedic referral rate (per 1000 practice population)<sup>c</sup> Pre intervention: 10.6 (study) vs 12.1 (control) Post intervention: 8.8 (study) vs 11.0 (control) Absolute difference (post): -2.2 referrals per 1000 practice population</p>	Not assessed.	<p>ORGANISATIONAL INTERVENTION (a) Intervention commenced 11/92 ie post intervention period only included 6 months of the intervention period. (b) Statistical testing not reported. (c) Within group analysis reported with probable unit of analysis error.</p>

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			Relative percentage difference: -20% Absolute difference from baseline: -1.8 referrals per 1000 practice population (study) vs -1.1 (control) Difference in absolute change from baseline: -0.7 referrals per 1000 practice population Rheumatology referral rate (per 1000 practice population) Pre intervention: 2.3 (study) vs 2.0 (control) Post intervention: 1.1 (study) vs 1.3 (control) Absolute difference (post): -0.2 referrals per 1000 practice population Relative percentage difference: -15.4% Absolute difference from baseline: -1.2 referrals per 1000 practice population (study) vs -0.7 (control) Difference in absolute change from baseline: -0.5 referrals per 1000 practice population		
Thomas 2000	5 months pre and 10 months post intervention	Guideline based fast track open access investigation service vs control	Proportion of patients referred through fast track system Post intervention 48.2% of eligible patients referred through new system. Number and case mix of referrals. No significant differences in referral rates or case mix	Out comes at 12 months No significant differences in SF36 MCS and PCS scores, HADS anxiety scale, AUA	EDUCATIONAL INTERVENTION (a) Data analysed using multilevel model after correcting for pre intervention data and clustering of patients within practices. Reported data derived from multilevel models rather than crude data. (b) Effect size= difference in

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>(based on SF36 and condition specific outcome measures) of patients referred with tracer conditions. a (study equivalent)                      Compliance with referral guidelines (score out of 5)                      Pre intervention: 2.7 (study) vs 2.8 (control)a                      Post intervention: 3.4 (study) vs 3.0 (control) (Effect size 0.5; 95% CI 0.21 to 0.81)b (study better)                      General practitioner pre and post referral workload                      No significant differences in number of consultations prior to and 12 months following referral. a, c                      Waiting time from referral until first appointment (days)                      Pre intervention: 98 (study) vs 103 (control)a                      Post intervention: 39 (study) vs 59 (control) (Effect size 0.7; 95% CI 0.55 to 0.89) d, e (study better)                      Probability of management decision reached after one hospital appointment                      Pre intervention: 0.55 (study) vs 0.57 (control)a                      Post intervention: 0.73 (study) vs 0.56 (control) (Effect size 5.8; 95% CI</p>	<p>score (BPH only).</p>	<p>means                      (c) Hypothesised direction unclear                      (d) Effect size = ratio of means.                      (e) See text about pre post reduction in control group. f )                      Effect size= odds ratio.                      OR&gt;1 indicates benefit from intervention                      (g) Waiting times adjusted for number of available new appointments and clinic sessions and pre and post intervention differences tested using an unpaired t test.                      Data also presented as a time series graph suggesting effect largely due to intervention.</p>

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>2.9 to 11.5)f (study better)                      Probability of discharge from consultant at 12 months                      Effect size 1.7; 95% CI 0.92 to 3.27) a, f (study better)                      Waiting time for all urology referrals Pre intervention: 24.3 weeks (g)                      Post intervention: 13.3 weeks                      Difference = 11 weeks (95% CI 7.1 to 15 weeks)                      Economic evaluation                      Total cost of intervention estimated to be £28,665 (annual cost £9,995 assuming 3 yearly guideline update cycle).                      Prostatism                      Post intervention mean general practice pre-referral costs per patient £78.87 (study) vs £72.89 (control)                      Difference = +£5.98 (95% CI -£11.20 to +£21.85)                      (control cheaper)                      Post intervention mean general practice post-referral costs per patient £126.35 (study) vs £178.13 (control)                      Difference = -£51.78 (95% CI -£160.52 to +£37.66)                      (study cheaper)                      Post intervention</p>		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			mean hospital costs per patient £158.88 (study) vs £239.24 (control) Difference = -£80.26 (95% CI -£150.00 to - £2.34) (study cheaper)		
			Post intervention mean patient travel costs per patient £21.54 (study) vs £25.11(control) Difference = -£3.57 (95% CI -£12.60 to +£5.17) (study cheaper)		
			Microscopic haematuria Post intervention mean general practice pre-referral costs per patient £80.46 (study) vs £77.03 (control) Difference = +£3.43 (95% CI -£6.63 to +£13.29) (control cheaper)		
			Post intervention mean general practice post-referral costs per patient £21.85 (study) vs £18.70 (control) Difference = +£3.15 (95% CI -£10.05 to +£16.95) (control cheaper)		
			Post intervention mean hospital costs per patient £222.94 (study) vs £267.73 (control) Difference = -£44.79 (95% CI -£70.14 to - £16.76) (study cheaper)		

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			Post intervention mean patient travel costs per patient £23.09 (study) vs £25.93 (control) Difference = -£2.84 (95% CI -£12.60 to +£5.17) (study cheaper)		
Vierhout 1995	12 months following	Joint consultation session vs control	General practitioner use of diagnostic tests a, b Laboratory tests: Post intervention: 1.4% (Study) vs 4.7% (Control) (p = NS) Absolute difference (post): -3.3% Relative % difference (post): -70.2% Radiography: Post intervention: 24.3% (Study) vs 22.7% (Control) (p = NS) Absolute difference (post): +1.6% Relative % difference (post): +7.0% General practitioner use of therapeutic measures a, b Medication: Post intervention: 22.2% (Study) vs 22.7% (Control) (p = NS) Absolute difference (post): -0.5% Relative % difference (post): -2.2% Injection therapy: Post intervention: 30.6% (Study) vs 11.7% (Control) (Chi square p < 0.001) Absolute difference (post): +18.9%	No significant differences in between study and control groups in subjective or objective patients' variables including functional status.'b Disorder free after one year: 35.4% (study) vs 23.7% (control) (p<0.05).	EDUCATIONALINTERVENTION (a) Analyses recalculated using Arcus Biostat. (b) Explicit hypotheses not stated (c) Authors' analysis, raw data not presented.

**Table 01. Summary of Results (Continued)**

Study	Measurement Period	Comparisons	Main Process Effect	Main Patient Outcome	Notes
			<p>Relative % difference (post): +161.5% Physiotherapy referral: Post intervention: 43.1% (Study) vs 42.2% (Control) (P = NS) Absolute difference (post): + 0.9% Relative % difference (post): +2.1% General practitioner referrals to orthopaedic surgeon a, b Post intervention: 35.4% (Study) vs 68.0% (Control) (P&lt;0.001 Chi square test) Absolute difference (post): -32.6% Relative% difference (post):-47.9%</p>		

**Table 02. Appendix 1**

**Outpatient referrals from primary care to secondary care (Update)**

**16 October 2007**

**(refer\* or consult\*) and outpatient\***

**GRAPHS AND OTHER TABLES**

**This review has no analyses.**

**INDEX TERMS**

**Medical Subject Headings (MeSH)**

**Family Practice [standards]; Primary Health Care [standards]; Referral and Consultation [standards]; Specialties, Medical**

**MeSH check words**

**Humans**

**COVER SHEET**

<b>Title</b>	<b>Interventions to improve outpatient referrals from primary care to secondary care</b>
<b>Authors</b>	<b>RW and JG developed the review protocol. CF developed the EPOC search strategy and additional Medline search strategies. EG undertook electronic searches. EG, JG,CF, CP and RW selected studies for inclusion in the review. EG, JG, RW, AM, CP and RT undertook data abstraction. JG drafted the paper. EG, CF, RW and RT commented on all drafts of the paper. For the update, AA and AM screened identified studies and JG was involved in the final selection. Data abstraction was done by AA, AM and MA.</b>
<b>Issue protocol first</b>	<b>1999/2</b>

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**Interventions to improve outpatient referrals from primary care to secondary care (Review)**

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<b>What's New</b>	<b>The search was updated in October 2007 and the review updated in Feb 2008.</b>
<b>Date new studies sought but none found</b>	<b>Information not supplied by author</b>
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# Chapter 3

## Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis

### Contributors to the manuscript

**Ayub Akbari (Masters Candidate):** Conceptualized the study, designed the study, wrote the protocol, developed the data collection form, piloted the data collection form, randomly audited data collection, randomly audited data entry, cleaned the data, performed the data analysis and wrote the manuscript.

**Jeremy Grimshaw (Thesis supervisor):** Provided expert opinion throughout the study and commented on the final manuscript.

**Dawn Stacey (Thesis supervisor):** Provided expert opinion throughout the study and commented on the final manuscript.

**Marcella Cheng-Fitzpatrick (Research assistant):** Helped with development of the data collection form, piloted the data collection form, collected the data and entered the data into excel spreadsheet.

**Tim Ramsay (Biostatistician):** Provided expert opinion on analysis of the data.

**William Hogg (Family Physician):** Was involved in the initial design of the study.

**Peter Magner (Nephrologist):** Was involved in the initial design of the study and provided guidance on appropriateness of referral.

**Robert Bell (Nephrologist):** Was involved in the initial design of the study.

**Jolanta Karpinski (Nephrologist):** Was involved in the initial design of the study.

**Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis**

**Abstract**

**Background:** Serum creatinine, the most widely used marker of kidney function, has been associated with late referral to nephrology for patients with chronic kidney disease. To improve referral patterns, estimated glomerular filtration rate (eGFR) was introduced in the Champlain LHIN region of Ontario, Canada in March 2009.

**Objective:** To explore the impact of eGFR reporting on appropriateness and total referrals from family practice to nephrology.

**Methods:** Interrupted time series based on retrospective chart review of all outpatient referrals to nephrology at The Ottawa Hospital for one year pre-eGFR reporting (March 07 2005 to March 06 2006) and one year post-eGFR reporting (March 07 2006 to March 06 2007). Regression analysis with autoregressive errors was used to estimate the impact of eGFR reporting on primary outcome measures: number and appropriateness of referrals.

**Results:** Of 5093 referrals received in the study periods, 4999 (98.2%) of the referral packages were retrieved and 2672 (53.5%) were referrals from family physicians for CKD. Time series analysis revealed, a relative increase in referrals for CKD by family physicians of 68.2%; (95% confidence interval: 65.3%, 71.2%,  $P < 0.01$ ) post-intervention and a relative

increase in total appropriate referrals of 64.1%; (95% confidence interval: 60.8%, 67.4%,  $P = 0.01$ ) with no significant change in proportion of appropriate referrals (-2.5%, 95% confidence interval: -34.0%, 28.6%,  $P = 0.56$ ). More elderly and female patients were referred following the introduction of eGFR reporting.

**Interpretation:** Reporting of eGFR appears to increase the number of both appropriate and inappropriate referrals. The increase in the number of appropriate referrals will likely increase nephrological workload which could be (partly) offset if inappropriate referrals could be reduced. Further research is needed to better understand the reasons for and to evaluate interventions to reduce inappropriate referrals.

# Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: an Interrupted time series analysis

## Introduction

Until recently, serum creatinine was utilized universally as an index of glomerular filtration rate (GFR) to identify and monitor chronic kidney disease (CKD) (1). Serum creatinine is dependent on several factors, the most important being muscle mass (1). Africans have a higher muscle mass than Caucasians and their serum creatinine is higher than Caucasians for the same degree of kidney function (2). Women as compared to men and elderly as compared to young adults tend to have lower muscle mass for the same degree of kidney function and thus their serum creatinine is lower (3, 4). Consequently, the utilization of serum creatinine is associated with under recognition of CKD, delayed workup of CKD, and late referral to nephrology particularly among women and the elderly. Late referral has been associated with increased mortality on dialysis (4-12).

In 1999 the Modification of Diet in Renal Disease (MDRD) formula was introduced for estimating GFR (13, 14). This formula utilized serum creatinine, age, gender and race (African or not) to calculate an estimated GFR (eGFR). All of these variables are easily available to laboratories except race. This was overcome by asking the requesting practitioner to multiply the result by 1.21 if the patient was African. Given that reporting eGFR markedly improves detection of CKD (15, 16), several international organizations

{American Society of Nephrology (in 2002) (17), Australasian Creatinine Consensus Working Group (in 2005) (18), the Renal Association in UK (in 2005) (19), Canadian Society of Nephrology (in 2006) (20)} recommended that laboratories automatically calculate and report eGFR when health care practitioners request a serum creatinine. These organizations also provided guidelines on appropriate referral to nephrology based upon eGFR results.

Three studies using interrupted time series analysis have assessed referral patterns to nephrology after the introduction of eGFR reporting. Richards et al. (21) reported a 170% increase in referrals from a Primary Care Trust in the UK 6 months post-eGFR reporting. Noble et al. (22) reported a 40% increase in outpatient referrals to nephrology in Queensland Australia 12 months post-eGFR reporting. Jain et al. (23) reported a 24% increase in referrals 21 months after eGFR reporting (utilizing administrative data) in the province of Ontario, Canada. The effect of eGFR reporting on the appropriateness of nephrological referrals was only assessed in the study by Noble et al. in Australia (22). They observed a significant fall in appropriateness of referral from 74.3 % pre-eGFR reporting to 65.2% post-eGFR reporting. They utilized Poisson regression to analyze their data and report incident rate ratios (IRR 0.63, 95% confidence interval: 0.48, 0.82,  $P < 0.05$ ). This analysis is limited as time series data are typically autocorrelated and the assumption of independence required for Poisson regression is violated which may cause spurious results (24). In addition their sample size (171 referrals in the pre- eGFR reporting period) was

small thus their data on appropriateness of referral is limited. Moreover the impact of eGFR reporting on appropriateness of referral has not been studied in the Canadian context of a single payer system. In summary, although studies have found an increase in referrals to nephrology post-eGFR reporting, little is known about the appropriateness of these referrals.

The aim of the current study was to evaluate the impact of introducing eGFR reporting along with educational activity on appropriateness of referral to nephrology by primary care physicians. Secondary objectives include determining the change in total number of referrals from family physicians and the completeness of referral package.

## **Methods**

### **Design**

A quasi-experimental study using interrupted time series analysis was used to estimate the effects of eGFR reporting on patterns and appropriateness of referral. Although randomized controlled trials provide the gold standard for assessing interventions (25), we could not perform a randomized controlled trial since the intervention was delivered simultaneously to the whole region. In an interrupted time series analysis, data are collected over multiple time points before the intervention to identify the underlying trend and after the intervention to determine the estimated effect of the intervention after

accounting for the underlying trend (24). The study was approved by The Ottawa Hospital Research Ethics Board.

### **Participants**

All patients referred by family physicians to nephrology at The Ottawa Hospital for one year pre-eGFR reporting (March 07 2005 to March 06 2006) and for one year post-eGFR reporting (March 07 2006 to March 06 2007) were included. Patients were excluded if they were referred from specialists, were already known to the nephrology service, or did not have CKD.

### **Setting**

The study was conducted at The Ottawa Hospital, a tertiary care academic teaching hospital with 18 nephrologists. It is the only nephrology centre in Ottawa and serves the majority of nephrological needs for the Champlain Local Health Integration Network (LHIN) with approximately 825 family doctors sending referrals. Referrals to two nephrologists that practice at a secondary care centre were not included in this study. The Champlain LHIN region of Eastern Ontario, Canada has a population of 1,176,600 (26). It is representative of the Canadian population with 12.5% of the population being 65 years or older, 17% being immigrants and 13% being visible minorities (26). Given the distance to other LHINs most individuals residing in Champlain LHIN receive health care within Champlain LHIN (26).

## **Intervention**

The primary intervention was the introduction of eGFR reporting which commenced in the first week of March 2006 in the Champlain LHIN. A new policy was introduced by the laboratories in Ontario to report eGFR along with serum creatinine when a serum creatinine was requested. This change affected all adult patients. All eGFR reports were provided with a laboratory prompt that included an explanation of eGFR ranges (see Table 2) (23).

Concurrent with the introduction of eGFR reporting, the nephrology program mailed an algorithm to all family physicians in the Champlain LHIN (see Appendix 2). This algorithm explained the interpretation of eGFR and appropriate parameters for referrals to nephrology based on eGFR. Ad hoc education sessions (lectures and workshops) were also provided to family physicians to discuss interpretation of eGFR results and parameters requiring referral to nephrology.

## **Procedures**

A trained research assistant (MC) extracted data from the referral package using a standard two-part data collection form developed for the study. The form was based on the Canadian referral guidelines (20) and designed in collaboration with experts in nephrology, family medicine, and epidemiology. Part I was designed to identify eligible referrals and included age and gender of patient and source of referral. Part II was

designed to capture data required to assess appropriateness of referral including reason for referral, changes in diagnostic tests, and contents of the referral package relevant to CKD. The form was pilot tested by having the research assistant (MC) and principal investigator (AA) independently extract data from 50 patient referral packages. Modifications made to improve accuracy and completeness of data collection included changes to reasons for referral as well as capturing of data on diagnostic tests.

The following complete set of data were collected about the patient on all new referrals from family physicians: a) date of referral; b) date of birth; c) sex; d) previous consultation with a nephrologist; e) reason for referral; f) whether or not the family physician stated that he/she was unable to achieve treatment targets; g) all serum creatinine results in the referral package within the 2 years of the date of referral; h) results for albumin to creatinine ratio, protein to creatinine ratio, 24 hour protein excretion, hemoglobin, calcium, phosphate, electrolytes (potassium), and urine analysis; and, i) report or request for imaging of kidneys.

The referrals were identified from the new referral spread sheet which is kept at the nephrology clinic of The Ottawa Hospital. All new referrals with their identification information are logged into this spreadsheet. During the main study, accuracy of data collection was verified by the principal investigator (AA) by independently extracting data on four key variables; a) whether inclusion and exclusion criteria were met; b) whether family physician indicated that treatment targets were not being met; c) values of all serum

creatinine and d) values of protein excretion. This verification was done on random sample of 5% of referral packages throughout the data collection period. There was 95% agreement between MC and AA on accuracy of data extraction. Agreement was calculated by determining the percentage of referrals in which there was no disagreement on any of the four variables between AA and MC.

## **Outcomes**

### **Appropriateness of referral**

A referral was defined as appropriate if: a) it met the criteria set by Canadian Society of Nephrology (table 1) (20) and/or b) the family physician provided a specific reason for referral such as hyperkalemia.

### **Completeness of referral package**

The referral package was defined as complete for referrals with eGFR  $\geq 30$  ml/min/1.73m<sup>2</sup> if it included; a) the results for more than one serum creatinine; b) results for urine analysis, electrolytes (potassium), hemoglobin, quantification of protein in the urine; and c) results of imaging of the kidney or statement indicating that it has been requested. The referral package was defined as complete for referrals with eGFR  $< 30$  ml/min/1.73m<sup>2</sup> if in addition to the definition above, it also included the results of calcium, phosphate and albumin.

## Statistics and Data Analysis

Data were entered into Microsoft Office Excel 2007 and then a SAS data set was made by Stat/ Transfer (version 9). Data entry was verified by auditing 5% of a random sample. There was 97% agreement between MC and AA on accuracy of data entry. Agreement was calculated by determining the percentage of patients in which there was no disagreement between AA and MC.

eGFR was calculated using the abbreviated MDRD formula for both time periods. The calculation did not account for African ethnicity as this information was not available on the referrals (14).

SAS enterprise guide (version 4.2) was utilized for all data analysis. Results are expressed as mean  $\pm$  SD and/or median with interquartile range (IQR) for continuous data and percentages and frequencies for categorical data. Comparisons of pre-eGFR reporting period with post-eGFR reporting period for continuous data were performed by independent two samples T-Test and for categorical variables by chi square test. Separate time series analyses were performed for changes in number of referrals for CKD from family physicians, appropriateness of referrals, and completeness of referral package. The Durbin-Watson statistic was utilized to test for autocorrelation. No significant autocorrelation was detected but since time series data are typically autocorrelated, we undertook a conservative approach and utilized regression analysis with autoregressive errors. Using the maximum likelihood method, we fitted a first-order autoregressive model

(27). The outcome measures (total number of referrals from family physicians for CKD, total number of appropriate referrals, proportion of appropriate referrals and, completeness of referral packages) were the dependent variables. To determine the expected number of the dependent variable in the year following exposure to the intervention, three variables were entered into the time series model (27); a) an indicator variable to differentiate between pre and post-eGFR reporting period; b) a time variable (1, 2, 3.....52, indicating bi-weekly time period of the study); and c) an interaction term (multiplication of a and b). The regression model is as follows.

$$Y_i = \alpha + (\beta_1 T_i) + (\beta_2 P_i) + (\beta_3 T_i P_i) + v_i$$

$$v_i = -\phi_1 v_{i-1} + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \sigma^2)$$

$Y_i$  is the response variable at time  $i$ ,  $\alpha$  is the intercept,  $T_i$  is the indicator variable, 0 or 1, 0 = pre-intervention and 1 = post-intervention,  $P_i$  is the time variable of the study (1,2,3.....52). This model thus augments the standard regression model with an autoregressive error structure ( $-\phi_1 v_{i-1} + \varepsilon_i$ ). Thus if there was no intervention ( $T_i = 0$ ), the model will be,  $Y_i = \alpha + \beta_2 P_i + v_i$ , where  $\beta_2$  is the parameter estimate of the time variable. The parameter estimate of the time variable ( $\beta_2$ ) was multiplied by the time variable 27 to 52 (the time variable of the year post-intervention period) and then added to the intercept ( $\alpha$ ) to give the expected number, every two weeks and this was added up to give the expected

number per year. The effect of intervention was calculated by subtracting the expected number from the observed number (See figure 1, where dotted line is the expected number and the solid lines are the observed numbers). To estimate confidence intervals, the squared standard error of the difference between observed and expected was computed by summing the squared standard errors of the individual difference estimates, following the principle that the variance of a sum of independent variables is equal to the sum of the variances. Given that autocorrelation was controlled for in the regression model, it is reasonable to assume that the individual difference estimates are independent. The p-value for the interrupted time series model was obtained by using a standard likelihood ratio test comparing that model's deviance to the deviance of the nested simple regression model.

The effect size for primary and secondary outcome measures was calculated by subtracting the estimated value from the observed value and dividing this number by the estimated value. The result was then multiplied by 100 to give the percentage value of the effect size  $\{(observed\ value - expected\ value) / (expected\ value)\} \times 100$ . This calculation gives the percentage change observed relative to expected value thus calculating the effect size of the intervention.

## **Results**

Of 5093 referrals to the Ottawa Hospital nephrology department in the study period, 4999 (98.2%) referral packages were retrieved for data extraction. Of 4999, 2421

referrals were excluded due to referral from specialists (n=1182), referrals previously known to the nephrology service (n =717), and referrals that were not for CKD (n=428) (see Figure 2). The only significant difference between excluded groups was in patients known to nephrology with higher proportion in the pre-eGFR period compared to post-eGFR period (4%, 95% confidence interval: 2.1%, 5.9%,  $P < 0.01$ ).

Characteristics of the patients referred for CKD by family physicians are shown in table 3. In the post-eGFR reporting period, there was a statistically significant higher proportion of patients referred who were over 80 years of age (8.0%, 95% confidence interval: 4.9%, 11.1%) and/or female (12.6%, 95% confidence interval: 8.8%, 16.4%). eGFR values at the time of referral were significantly lower in the post-eGFR reporting period (4.5 ml/min/1.73m<sup>2</sup>, 95% confidence interval: 2.7 to 6.2). There were no statistically significant differences between groups for serum creatinine or proteinuria (see table 3).

Time series analysis revealed a relative increase in referrals for CKD post-eGFR reporting by family physicians of 68.2% (95% confidence interval: 65.3%, 71.2%,  $P = <0.01$ ; table 4, figure 3). There was also a relative increase in the number of appropriate referrals of 64.1% (95% confidence interval: 60.8%, 67.4%,  $P = 0.01$ ; table 4, figure 4) with no significant change in proportion of appropriate referrals (-2.5%, 95% confidence interval: -34.0% , 28.6%,  $P = 0.56$ ; table 4, figure 5). Figure 5 indicates that the proportion of appropriate referrals fell in the first two weeks after initiation of eGFR reporting and then rose gradually until the end of the year when it was higher than the pre-eGFR reporting

level. Examining subgroups based on eGFR, there was an increase in the completeness of referral package for referrals with eGFR  $\geq 30$  ml/min/1.73m<sup>2</sup> of 91.4% (95% confidence interval: 81.0%, 100%,  $P = 0.02$ ; table 4, figure 6) and no significant change in the completeness of referral package for eGFR  $< 30$  ml/min/1.73m<sup>2</sup> (-25%, 95% confidence interval: -50.0% , 0.0%,  $P = 0.27$ ).

Determinants of appropriate referrals are listed in Table 5. Post-eGFR reporting, more referrals were received for patients with eGFR results  $< 30$ ml/min/1,73m<sup>2</sup> ( $P < 0.01$ ) but there was no significant difference based on proteinuria, progressive CKD or specific issues raised by family physicians (see Table 5). Elements associated with completeness of referral package are listed in table 6 and 7. In the pre and post-eGFR reporting period, we could not calculate eGFR on 70 (5.8%) and 113 (7.7%) of referrals respectively ( $P = 0.08$ ) as no serum creatinine was provided with the referral. Urine analysis and imaging of kidneys were significantly more likely to be performed in the post-eGFR reporting period for patients with eGFR  $\geq 30$  ml/min/1.73m<sup>2</sup> and quantification of protein in urine was more likely to be performed post-eGFR reporting in patients with eGFR  $< 30$  ml/min/1.73m<sup>2</sup>.

## **Discussion**

In our study, automated eGFR reporting along with adhoc educational activities was associated with increased number of referrals to nephrology. We observed increased absolute number of appropriate referrals but the proportion of appropriate referrals did not change as number of inappropriate referrals also increased. The referral packages were

more complete post-eGFR reporting for  $eGFR \geq 30 \text{ ml/min/1.73m}^2$  but overall were low (7.6%).

Automated eGFR reporting was introduced to improve detection and referral of CKD as serum creatinine alone was associated with delayed referral to nephrology especially for the elderly and women (4-12). With this intervention there was a concern that inappropriate referrals to nephrology would increase (28, 29). Our study is the first to document with a robust methodology the increased number of appropriate referrals to nephrology. Although the proportion of appropriate to inappropriate referrals did not change, the time series plot indicated that the proportion of appropriate referrals fell in the first two weeks after exposure to the intervention and then rose gradually until the end of the year. It is not clear if this trend is sustained beyond this year. The initial fall in proportion of appropriate referrals might be ascribed to the new test being introduced for which family physicians were unfamiliar and the time for adjusting to the practice change. The increase in appropriate referrals post-eGFR reporting will potentially improve patient care and health service providers should devise means to deliver the appropriate services for these patients. To our knowledge, the only other study that reported on appropriateness of referral was the study by Noble et al. (22). Similar to this study, they found an absolute increase in appropriateness of referral of 15 per month to 24 per month post-eGFR comparing 3 months pre-intervention period to 12 months post-intervention period. In contrast to our study, that found no significant change, Noble et al. reported that

the proportion of appropriate referrals decreased. It is conceivable that their results are different than ours because they did not correct for autocorrelation (25). Other hypotheses for the difference observed may relate to difference in sample size, differences in the study population, geographical location, as well as classification criteria for appropriate referral.

In our study, as well as the study by Noble et al. (22) a substantial number of referrals were considered inappropriate using the referral guidelines developed by the respective societies (18, 20). Increase in inappropriate nephrology referrals in Canada will have a major impact on health service deliveries to Canadians. It will increase wait time for nephrology consultation thus delaying care to patients who need urgent attention as well as increase cost to the system since specialist care is more costly. Factors that may be responsible for inappropriate referrals may include; a) lack of knowledge about appropriate referrals; b) lack of resources to manage patients with mild CKD in primary care; c) patient demand to see specialist; and d) different perspectives about what constitutes an appropriate referral (30, 31). A recent Cochrane review indicated that passive diffusion of guidelines is unlikely to lead to improvements in referral behavior. Local dissemination and implementation activities appear necessary and more specifically if local secondary care providers are involved, the referral process improves (32). Our data regarding increased number of appropriate referrals are consistent with these findings. Therefore more concentrated effort needs to be made to improve family physicians behavior regarding appropriate referrals. Further research may help to delineate the reasons for inappropriate

referral (32). Interventions to decrease inappropriate referrals would help to limit the total number of consults to nephrology thus limiting the impact of the increased workload.

A complete referral package facilitates more efficient and accurate triaging of patients and use of time during the specialist consultation, thereby reducing repeat visits. The quality of referral package has been studied by several investigators (33-37) and investigators have consistently reported dissatisfaction of specialists with the quality and content of the referral letters (38). In our study the completeness of referral package for  $eGFR \geq 30 \text{ ml/min/1.73m}^2$  improved by 90%. Although this is a marked increase in percentage, the absolute numbers were quite small with the expected number being only 58 referrals which improved to 111 referrals post-intervention. Despite provision of education regarding completeness of referral package, 92.2% of referrals did not have a complete referral package. Further research is needed to find ways of providing appropriate information to a consultant prior to visit.

The number of consults from family doctors for CKD increased by 68.2% indicating improved detection of CKD. Our data indicates that most of the increase in referrals was for elderly and females which is consistent with the findings of Jain et al. (23) and Noble et al. (22). Several studies have shown the poor performance of serum creatinine alone in screening for CKD especially in the elderly and female (3, 4, 15). With the increasing age of the population, this is an important finding.

Strengths of our study include the large sample size and the robust methodology employed. The biggest threat to time series analysis is an event that independently has similar effect to the intervention at the time point of the intervention (24). It is highly unlikely that the number of patients would have abruptly increased at the time of intervention. Moreover Jain et al. (23) observed no change in consults to dermatology in Ontario in their analysis during the same era. A second common threat to time series analysis is seasonal trend. Since we collected data for one year pre and one year post-eGFR reporting, we consistently captured potential seasonal variations in referral to nephrology in both time periods. A third threat to time series analysis is a change in the way records are kept. During the time period studied, there was no known change in administrative process in tracking of nephrology referrals at the Ottawa Hospital (24).

Four limitations to our study should be noted. First data were collected retrospectively. However, using this approach we were able to retrieve 98% of referral packages and ensured data were collected on “all” consults received. Second, although our study is limited to a single centre, most patients are referred to this centre given that 90% of nephrologists are employed there and it serves a diameter of 250 kilometers. Third the educational interventions were not studied independently from the automated eGFR reporting. Although this would have provided information about the effect of each intervention individually, we do not believe that an intervention in laboratory reporting should be undertaken without appropriate education of the target audience. Finally, we

calculated eGFR by the MDRD formula without accounting for race. This should not have a major impact as only 3.9% of the population of Ontario is of African origin and the same approach was used for both time periods (39).

## **Conclusion**

Automated eGFR reporting along with *ad hoc* educational activities was associated with an increased total number of referrals and number of appropriate referrals. Although appropriateness improved, there continues to be a large number of inappropriate referrals. As well, completeness of referral package for  $eGFR \geq 30 \text{ ml/min/1.73m}^2$  increased but in absolute numbers it remained low. Future research should be directed to understanding the reasons for inappropriate referral as well as to develop novel interventions for improving the referral process.

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**Table 1. Canadian Society of Nephrology Recommendations for Referral to Nephrologist (20)**

1. Acute renal failure
2. eGFR < 30 ml/min/1.73m<sup>2</sup>
3. \*Progressive loss of kidney function
4. Persistent proteinuria on dipstick, or quantified protein to creatinine ratio (PCR) > 100 mg/mmol or urine albumin to creatinine ratio (ACR) > 60 mg/mmol.
5. If the practitioner is unable to achieve treatment targets for blood pressure, is unable to maintain the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers or other renal protective or cardiovascular protective strategies, or feels otherwise sufficiently unprepared to manage the CKD patient.

\*Progressive loss of kidney function was defined locally as > 20% fall in eGFR within one year

**Table 2. Typical eGFR reporting laboratory prompts**

eGFR* $\geq$ 90	Normal eGFR
eGFR* 60-89	Slightly reduced eGFR is seen in approximately 30% of adults 20 years or older. Rule out kidney damage in patients with high risk for chronic kidney disease.
eGFR* 30-59	Consistent with moderate chronic kidney disease if result confirmed by repeat measurement, with persistence for 3 months or more.
eGFR* 15-29	Consistent with severe chronic kidney disease
eGFR* < 15	Consistent with kidney failure

eGFR, estimated glomerular filtration rate.

All reports were followed by: for African Americans, the reported eGFR should be multiplied by a factor of 1.21 and re-interpreted accordingly.

\*eGFR calculated by abbreviated MDRD equation in ml/min/1.73m<sup>2</sup>.

Source: reference 22.

**Table 3. General Characteristics of Patients Referred by Family Physicians to Nephrology**

	Pre-eGFR Reporting n=1207	Post-eGFR Reporting n=1465	Difference (95% CI)	P value
<b>Age</b>				
Age, data available	100%	100%		
Age (years), Median (IQR)	68.9 (55.2-80)	71.2 (58.4-80.2)		
Age (years), Mean $\pm$ SD	65.4 $\pm$ 16	67.9 $\pm$ 16	-2.4 (-1.2, -3.6)	<0.01
Age < 50 years, %	18.2	14.9	3.3 (0.5, 6.2)	0.02
Age 50-64 years, %	22.5	21.1	1.4 (-1.7, 4.6)	0.4
Age 65-79 years, %	41.8	38.5	3.3 (-0.5, 7.0)	0.1
Age $\geq$ 80 years, %	17.5	25.5	8.0 (4.9, 11.1)	<0.01
<b>Gender</b>				
Gender, data available, %	100	100		
Females, %	41.7	54.3	12.6 (8.8, 16.4)	<0.01
<b>Serum creatinine</b>				
Serum creatinine, data available, %	94.2	92.3	1.9 (0.0, 3.8)	0.06
Serum creatinine ( $\mu$ mol/L), Median, (IQR)	133 (105-166)	135 (109-168)		
Serum creatinine ( $\mu$ mol/L) Mean $\pm$ SD	140.6 $\pm$ 54.8	144.3 $\pm$ 55.8	-3.7 (-8.1, 0.7)	0.1
Serum creatinine > 150 ( $\mu$ mol/L), %	36.7	36.4	0.3 (-3.5, 4.1)	0.92
Serum creatinine $\leq$ 150 ( $\mu$ mol/L), %	63.3	63.6	0.3 (-3.5, 4.1)	0.92
<b>eGFR</b>				
eGFR, data available, %	94.2	92.3	1.9 (0.0, 3.8)	0.06
eGFR (ml/min/1.73m <sup>2</sup> ), Median, (IQR)	44.7 (33.3-59.7)	41.8 (30.7-54.6)		
eGFR (ml/min/1.73m <sup>2</sup> ), Mean $\pm$ SD	49.9 $\pm$ 23.6	45.4 $\pm$ 20.6	4.5 (2.7, 6.2)	<0.01
eGFR < 30 ml/min/1.73m <sup>2</sup> , %	18.7	23.8	5.1 (1.9, 8.3)	<0.01
eGFR 30-59 ml/min/1.73m <sup>2</sup> , %	56.6	58.9	2.3 (-1.7, 6.1)	0.3
eGFR $\geq$ 60 ml/min/1.73m <sup>2</sup> , %	24.5	17.3	7.2 (4.0, 10.4)	<0.01
<b>Proteinuria</b>				
Proteinuria, data available, %	48.7	47.6	1.1 (-2.7, 5.0)	0.6
Proteinuria (mg/day), Median (IQR)	170 (80-454)	145 (45-440)		
Proteinuria (mg/day), Mean $\pm$ SD	581.6 $\pm$ 1470	568.0 $\pm$ 1207	13.6 (-132.9, 160.2)	0.86

**Table 4. Primary and secondary outcome measures**

	Observed in the year post intervention	Expected in the year post intervention	Difference between observed and expected (95% CI)	Effect size of intervention (percentage Change above expected number) (95% CI)	P value
Total number of consults from family physicians for CKD	1465	871	594 (569, 620)	68.2% (65.3%, 71.2%)	<0.01
Total number of appropriate referrals	799	487	312 (296, 328)	64.1% (60.8%, 67.4%)	0.01
Proportion of appropriate referrals	0.545	0.559	-0.014 (-0.19, -0.16)	-2.5% (-34.0%, 28.6%)	0.56
Referral packages complete for referrals with eGFR $\geq$ 30	111	58	53 (47, 58)	91.4% (81.0%, 100%)	0.02
Referral packages complete for referrals with eGFR $\leq$ 30	3	4	-1 (-2, 0)	-25% (-50.0%, 0.0%)	0.27

**Table 5. Elements of Appropriate Referral**

	Pre-eGFR reporting	Post-eGFR reporting	Difference (95% CI)	P value
eGFR < 30 ml/min/1.73m <sup>2</sup>	214 (18.8%) (n=1137)*	322 (23.8%) (n=1352)*	5.0 % (1.8, 8.2)	<0.01
Proteinuria > 1 gm/day	85 (14.5 %) (n=588)*	113 (16.2%) (n=697)*	1.7% (-2.2, 5.7)	0.4
Progressive CKD	150 (22.7%) (n=661)♥	185 (23.2%) (n=796)♥	0.5% (-3.8, 4.9)	0.9
FMD unable to achieve treatment target	49 (4.1%) (n=1207) <sup>σ</sup>	77 (5.3%) (n=1465) <sup>σ</sup>	1.2% (-0.4, 2.8)	0.2
Specific question by FMD	397 (32.9%) (n=1207) <sup>σ</sup>	427 (29.2%) (n=1465) <sup>σ</sup>	3.7% (0.2, 7.3)	0.04

\*Number of referrals where eGFR could be calculated

\*Number of referrals where quantification of protein excretion was performed

♥Number of referrals where determination of progressive CKD was possible

<sup>σ</sup>Total number of referrals

**Table 6. Elements in the referral Package For eGFR  $\geq$  30 ml/min/1.73m<sup>2</sup>**

	Pre-eGFR reporting* n=923	Post-eGFR reporting <sup>^</sup> n=1030	Difference (95% CI)	<i>P</i> value
More than 1 serum creatinine	519 (56.2%)	599 (58.2%)	2% (-2.5, 6.3)	0.42
Urine analysis, %	432 (46.8%)	542 (52.6%)	5.8% (1.4, 10.3)	<0.01
Quantification of Protein in urine, %	518 (56.1%)	564 (54.8%)	1.3% (-3.1, 5.7)	0.6
Imaging of kidney, %	351 (38.0%)	454 (44.1%)	6.1% (1.7, 10.4)	<0.01
Electrolytes (K), %	699 (75.7%)	803 (78.0%)	2.3% (-1.5, 6.1)	0.3
Hemoglobin, %	671 (72.7%)	794 (77.1%)	4.4% (0.6, 8.3)	0.03

\*Total referrals in pre-eGFR reporting period were 1207. In 70 (5.8%) referrals, eGFR could not be calculated.

<sup>^</sup>Total referrals in post-eGFR reporting period was 1465. In 113 (7.7%) referrals, eGFR could not be calculated.

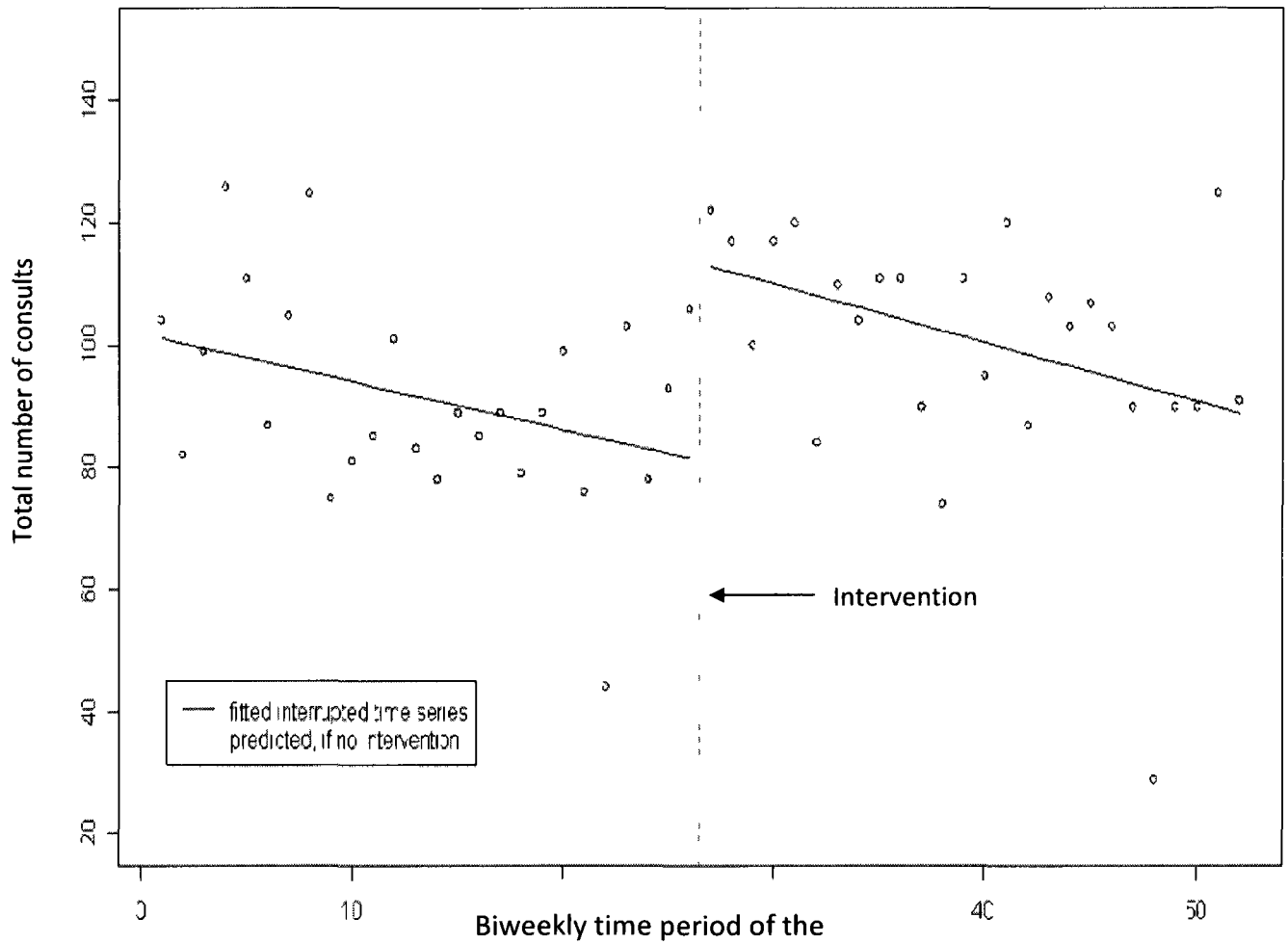
**Table 7. Elements in the referral package with eGFR < 30 ml/min/1.73m<sup>2</sup>**

	Pre-eGFR reporting* n=214	Post-eGFR reporting^ n=322	Difference (95% CI)	P value
More than 1 serum creatinine	142 (66.4%)	197 (61.2%)	-5.2% (-3.1, 13.5)	0.27
Urine analysis	77 (36.0%)	117 (36.3%)	0.3% (-8.0, 8.7)	1.0
Quantification of Protein in urine	49 (22.9%)	101 (31.4%)	8.5% (0.9, 16.0)	0.04
Imaging of kidney	87 (40.7%)	116 (36.0%)	-4.7% (-3.8, 13.0)	0.3
Hemoglobin	166 (77.6%)	241 (74.9%)	-2.7% (-4.6, 10.1)	0.53
Electrolytes (K)	179 (83.7%)	248 (77.0%)	-6.7% (-0.1, 13.4)	0.08
Calcium	43 (20.1%)	65 (20.2%)	0.1% (-6.8, 7.0)	0.93
Phosphate	30 (14.0%)	52 (16.2%)	2.2% (-4.0, 3.3)	0.58
Albumin	35 (16.4%)	63 (19.6%)	3.2% (-3.4, 9.8)	0.41

\*Total referrals in pre-eGFR reporting period were 1207. In 70 (5.8%) referrals eGFR could not be calculated.

^Total referrals in post-eGFR reporting period was 1465. In 113 (7.7%) referrals eGFR could not be calculated.

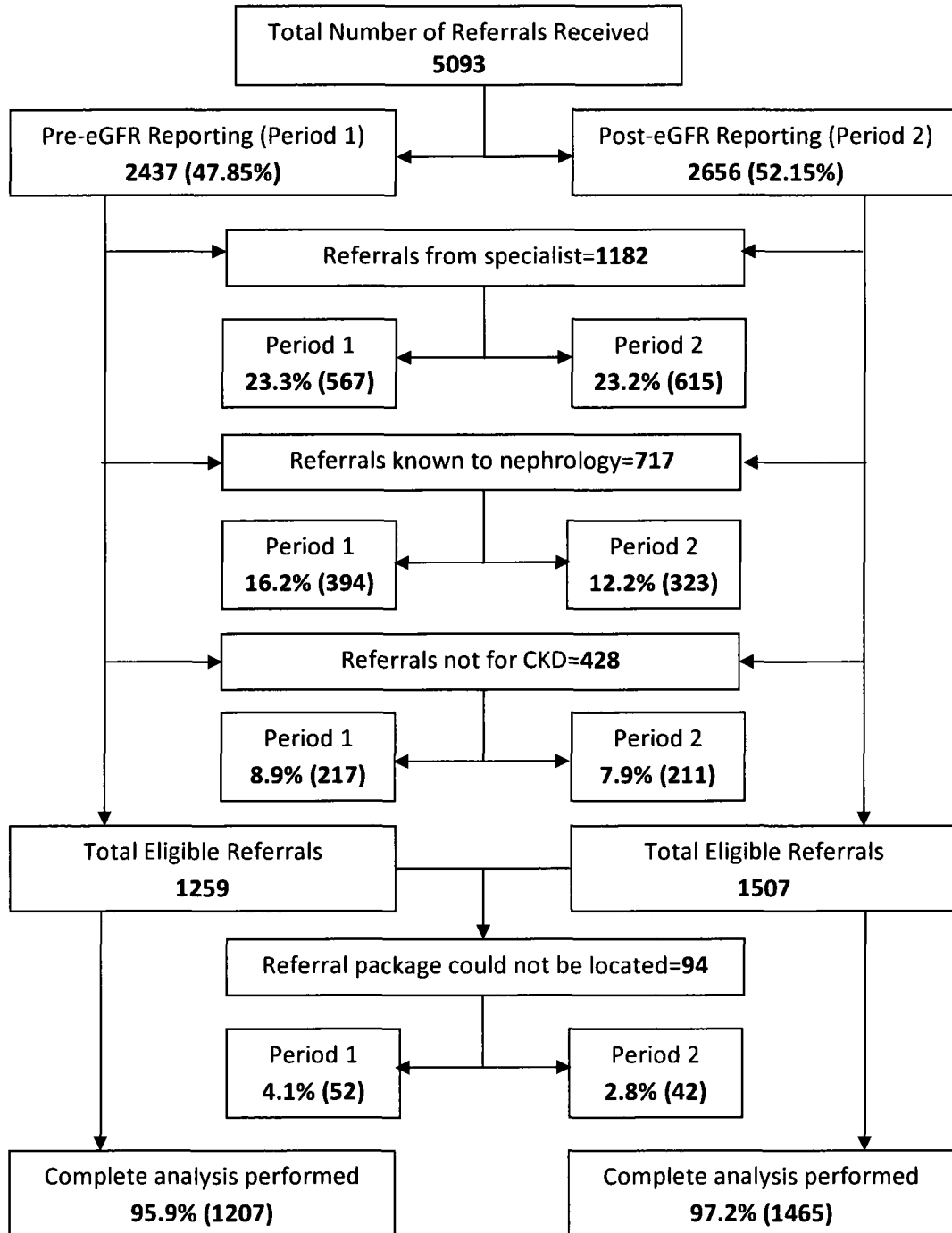
**Figure 1.** Example of calculation of difference between pre and post-intervention



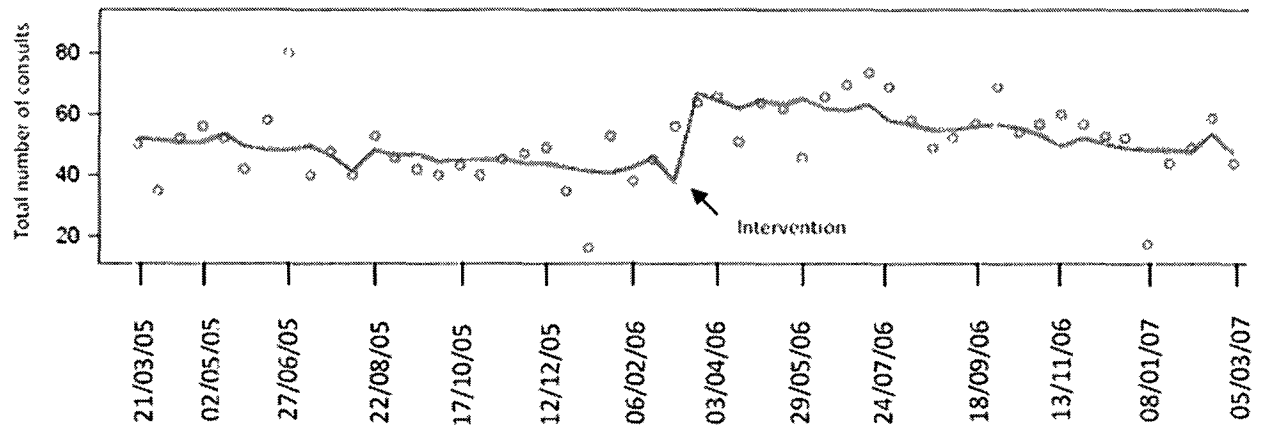
Open circles indicate observed number of consultations. Difference in number of consultations was calculated by subtracting observed number post-intervention from predicted number (dashed line) at biweekly intervals.

Figure 2.

Reasons for Exclusion



**Figure 3. Total number of consultations for chronic kidney disease from family physicians pre and post-intervention**



**Figure 4. Total number of appropriate consults for chronic kidney disease from family physicians pre and post-intervention.**

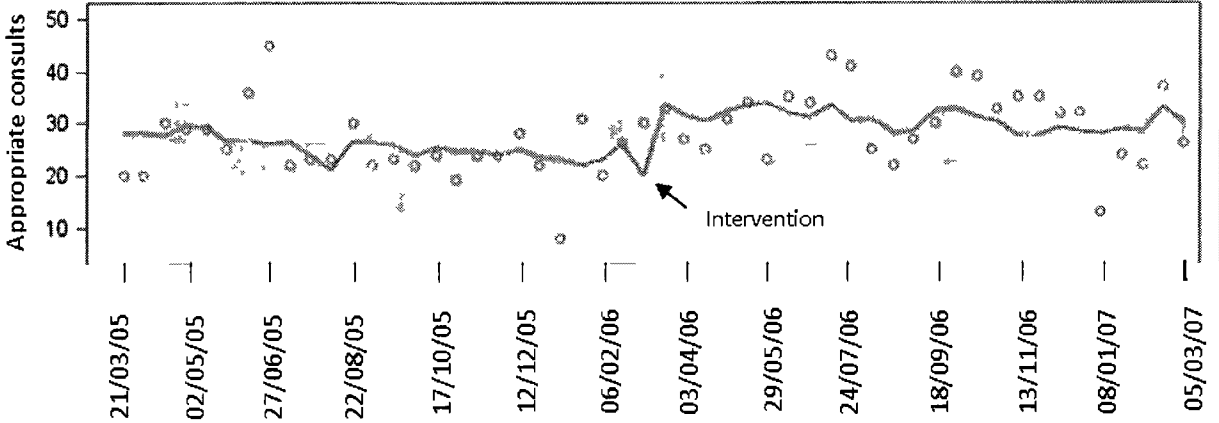


Figure 5. Proportion of appropriate consults for chronic kidney disease from family physicians

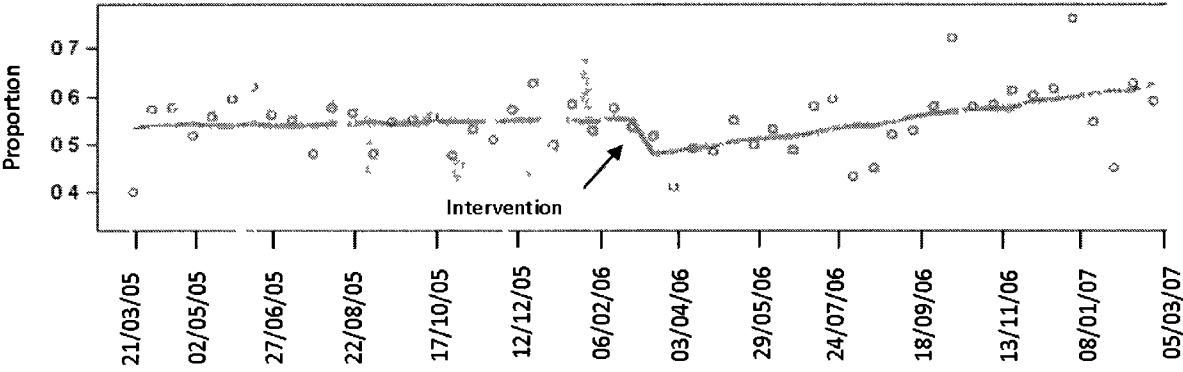
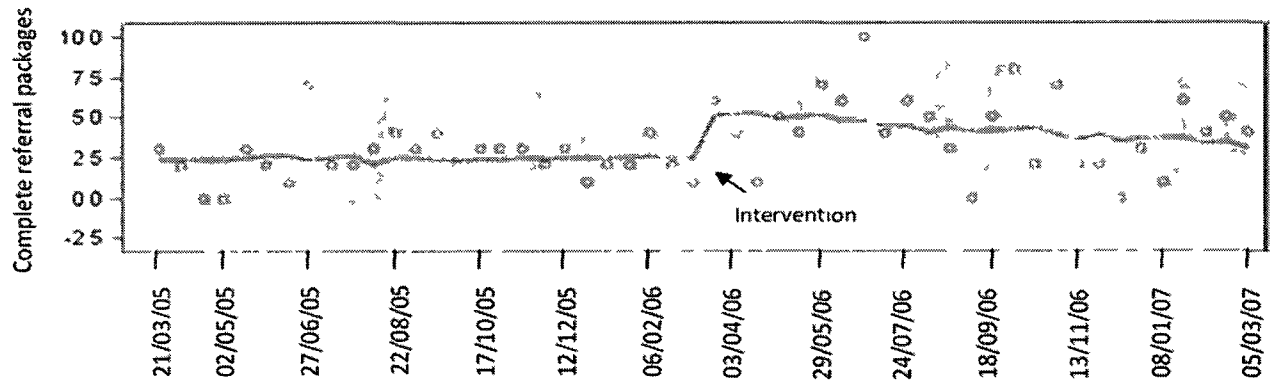


Figure 6. Complete referral packages received for referrals for chronic kidney disease with  $eGFR \geq 30 \text{ ml/min/1.73m}^2$



# **Chapter 4**

## **Integrated Discussion**

## Chapter 4

### Integrated discussion

#### 1.0 Key findings of the studies

#### 1.1 Key findings (Chapter 3) “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis”

Automated eGFR reporting was associated with an increase in total referrals (68.2%, 95% confidence interval: 65.3%, 71.2%,  $P < 0.01$ ) and an increase in appropriate referrals (64.1%, 95% confidence interval: 60.8%, 67.4%,  $P = 0.01$ ). However the proportion of appropriate referrals of the total referrals was not significantly different (-2.5%, 95% confidence interval: -34.0%, 28.6%,  $P = 0.56$ ) because of an increased number of inappropriate referrals. The increase in total referrals was because of 8% (95% confidence interval: 4.9%, 11.1%,  $P < 0.01$ ) increase in referrals for the elderly (age  $\geq 80$  years). There was also a 12.6% (95% confidence interval: 8.8%, 16.4%,  $P < 0.01$ ) increase in referrals for females. The completeness of referral package improved for referrals where eGFR was  $\geq 30$  ml/min/1.73m<sup>2</sup> (90%, 95% confidence interval: 81.0%, 100%,  $P = 0.02$ ) but still remained disappointingly low with only 7.8% referrals packages being complete in the post-intervention period. Figure 5 in chapter 3 indicates that the proportion of appropriate

referrals fell in the first two weeks after initiation of eGFR reporting and then rose gradually until the end of the year when it was higher than the pre-eGFR reporting level.

## **1.2 Key findings (Chapter 2) “Interventions to improve outpatient referrals from primary care to secondary care”**

One new study (1) was included in the updated systematic review and one study (2) was removed as it was a controlled before and after study with one intervention and one control site which did not meet the updated Effective Practice and Organisation of Care Group (EPOC) inclusion criteria for controlled before and after study (3). The updated criteria for inclusion of controlled before and after study by Cochrane collaboration is that the study should have at least two intervention sites and two control sites (3).

The updated systematic review again found limited number of studies to base conclusions on. Seventeen studies with twenty three comparisons were eligible for inclusion in the review. Nine studies (14 comparisons) evaluated professional educational interventions, four studies evaluated organizational interventions and four studies evaluated financial interventions. Active local educational interventions involving secondary care specialists and structured referral sheets were the only interventions which impacted referral rates. The effects of ‘in house’ second opinion and other intermediate primary care based alternatives to outpatient referral showed promising results. Financial interventions showed mixed results. Passive diffusion of local referral guidelines, feedback

of referral rates and discussion with an independent medical adviser was not effective. There was no change in the key findings as compared to the previous review (4).

## **2.0 Strengths and weaknesses of the studies**

### **2.1. Strengths of the study (Chapter 3) “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis”**

We assessed 4999 (98.2%) out patient referrals out of a total of 5093 out patient referrals received over the study period (two years) at the nephrology division of the Ottawa Hospital. This division serves the majority of nephrological needs of the Champlain Local Health Integration Network (LHIN) of eastern Ontario which has a population of 1,176,000 and is representative of the Canadian population. Thus we were able to capture data for a substantial population base. We reviewed every referral retrospectively to determine appropriateness of referral as per guidelines developed by Canadian Society of Nephrology which were consistent with local guidelines thus capturing data on appropriate referral for every referral from family doctor (5, 6). We ensured accurate data extraction by developing a specific data extraction sheet for the study and modifying it after pilot testing the data extraction sheet. We performed quality control on 5% randomly selected referrals

with duplicate data extraction. Data entry was also verified on 5% of entries. Thus we attempted to minimize any errors in data extraction and entry.

We utilized the simple interrupted time series (ITS) design as the intervention was introduced at a specific point in time and we studied the impact of intervention comparing it to the time period before intervention. Randomized controlled trials are the 'gold standard' for evaluating health care interventions as randomisation creates two groups that are probabilistically similar to each other on average and thus any intervention can be tested without confounding as on the average the two groups would be similar in all aspects except the intervention (7). However in our setting it was not possible to do a randomized controlled trial as we did not have any control over the intervention. A one group pre-test post-test design would have been inferior for our study as this design would neglect trends that might have been present before the intervention and thus may give spurious conclusions (7). In an interrupted time series analysis, data are collected over multiple time points before the intervention to identify the underlying trend and after the intervention to determine the estimated effect of the intervention after accounting for the underlying trend (7). The major threat to internal validity of simple ITS is the threat of history, the possibility that a simultaneous event other than intervention lead to the changes observed. In our study this is unlikely as kidney disease would not have become more prevalent suddenly in the year post-intervention nor number of patients seen by family doctors would have increased in an abrupt fashion. Another threat to ITS validity is

instrumentation. This threat is again unlikely in our study as definition of chronic kidney disease remained the same pre and post-eGFR reporting. Another threat is simple selection which again is unlikely to affect our results as it is unlikely that a sudden change occurred in composition of physicians in the area. A final threat to validity is cyclical variation of the variable. We obtained data one year pre and one year post-eGFR reporting and thus took into account when physicians would take vacations in both time periods (7).

The basic approaches to statistical analysis of time series data are; a) smoothing methods; b) decomposition models; c) Box-Jenkins time series models (including autoregressive integrated moving average model (ARIMA)) and d) autoregression models. Smoothing methods are good for short term forecasting (8). As we had one year post-intervention data, we needed one year forecast of referrals to compare to what was observed and smoothing methods would not have been appropriate. Decomposition models are mainly used for cyclical data such as seasonal effects and our data did not show cyclical patterns. Box-Jenkins time series models (ARIMA) (9) is the recommended approach to analyzing time series data but typically at least 50-100 observations are required for an adequate model (7) and we only had 24 observations pre-intervention and thus utilizing Box-Jenkins time series model would have been numerically unstable (8). Time series data are typically autocorrelated and utilizing ordinary regression would have violated the assumption of independence (an assumption for ordinary least squares regression) which would have resulted in standard deviation of parameter estimates to be

biased and thus the  $P$  values would be biased. Thus we used regression analysis with autoregressive errors for forecasting the expected values. Regression models forecast better than other techniques over medium and long run (8). To investigate the impact of intervention, we calculated the percentage difference between expected and observed value thus estimating the effect of the intervention.

## **2.2 Weaknesses of the study (Chapter 3) “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis”**

We obtained data retrospectively from notes sent by family physicians and thus it is possible that the package did not contain all data that was available to the family physicians such as quantification of protein in the urine and decline in kidney function data. It is also possible that the family physician did not state the reason for referral on the referral sheet and he/she had a valid reason for referral. We could not locate 2.8% of the referrals. We obtained data one year pre and one year post-eGFR reporting. A longer period would have led to more robust conclusions and would have allowed us to use ARIMA modelling. ITS design does not protect against gradual intervention but the intervention studied was at one point and time (7). We could have strengthened our design by also doing a time series analysis on referral to an unrelated specialty such as dermatology but we did not have data to do this kind of analysis. It should be noted that Jain et al. (10) performed analysis on referral to dermatology in the province of Ontario and

did not find a difference after eGFR reporting. We could not separate the impact of education from eGFR reporting as education was an ongoing process.

### **2.3 Strengths of the study (Chapter 2) “Interventions to improve outpatient referrals from primary care to secondary “**

We updated the original review (4) which was performed by Cochrane methodology which is superior to traditional reviews (11). In our update, we also applied the Cochrane methodology. We performed a comprehensive literature search of key databases including EPOC, Medline and UK National Research Register. The search strategy was developed by CF, an expert in this field. We performed duplicate screening of abstracts and obtained full article if any of the abstract was judged by any one reviewer to have the potential for inclusion. For inclusion of studies in the systematic review, we adhered to the EPOC standard (3). Each study was evaluated for its quality in a standard format utilizing EPOC criteria. Data abstraction was done in duplicate so as to prevent errors. In addition we reviewed the methodology of studies included in the previous review (4) to make sure that reviews included still met the updated EPOC criteria for inclusion (3). Adhering to these guidelines should minimize the risk of missing a potential study as well as minimizing the risk of bias in the systematic review. Our systematic review has undergone peer review and was published as a Cochrane review (12).

## **2.4 Weaknesses of the study (Chapter 2) “Interventions to improve outpatient referrals from primary care to secondary care”**

A selection bias might have occurred in our systematic review (or any other review) as non published data are not available from all sources and it is well known that studies that do not have positive outcomes are less likely to be written up and published (13, 14). The other weakness of systematic review is the dependence of conclusion of the systematic review on the quality and quantity of studies included in the review (14). Our review is based on limited number of studies and limited evaluation of interventions. More over the majority of studies included had methodological short comings. Based on the heterogeneity of included studies we could not perform a meta-analysis and thus are unable to comment on the over all impact of particular intervention.

## **3.0 Strengths and weaknesses in relation to other studies**

### **3.1 Strengths and weaknesses in relation to other studies (Chapter 3) “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis”**

Jain et al. (10) only reported effects on the number of referrals using administrative data base. While this may be important for planning purposes, the appropriateness and quality of referral is more important from a population health prospective. Richards et al.

(15) in addition to reporting number of referrals commented on quality of referral which improved but did not quantify the impact. It is also unclear from their report how they determined appropriateness of referral. Noble et al. (16) assessed appropriateness of referral 3 months pre-eGFR reporting and compared it to 12 months post-eGFR reporting. Their pre-intervention time period is much shorter than ours which is 12 months and Noble et al. had only 171 referrals pre-intervention from all sources compared to our study which has 1207 referrals from family physicians prior to intervention. Moreover Noble et al. had zero patients referred pre-eGFR reporting for progressive kidney disease as compared to our study which has 150 such referrals. The study of Noble et al. was conducted in a setting where private health care is available whereas we conducted our study in a single payer environment and thus our study is more relevant to the Canadian system. Noble et al. applied Poisson regression to quantify their effect on appropriateness of referral. Time series data are typically autocorrelated and thus the assumption of independence is violated which may give biased results (7). We utilized regression analysis correcting for autoregressive errors (8, 17). Thus our analysis is more robust as it corrects for autocorrelation. Moreover none of the studies commented on completeness of referral package which is important to improve efficiency of the system especially when health care costs are increasing and number of consults to nephrology has increased. Our study is the first study in nephrology to comment on completeness of referral package post-eGFR reporting.

### **3.2 Strengths and weaknesses in relation to other studies (Chapter 2) “Interventions to improve outpatient referrals from primary care to secondary care”**

There was only one new study that could be added to our updated systematic review suggesting that this is not an active area of research. In addition there were no studies in the field of nephrology on the topic. Since our systematic review, there have been several studies in nephrology which would qualify for the update of the review.

### **4.0 Meaning of the studies: possible mechanisms and implications for clinicians and policy makers**

#### **4.1 Meaning of the study (Chapter 3): possible mechanisms and implications for clinicians and policy makers “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis”**

Our study indicated that laboratories reporting eGFR led to increased number of referrals to nephrology predominantly in elderly and women, a group previously under diagnosed (18, 19) and under referred (19). Thus it achieved the objectives of increasing referral in this group of patients. The total number of appropriate referrals also increased. Thus post-eGFR reporting there is higher likelihood that those who need it may receive better management of their kidney disease. Increase in total referrals has workload implications for nephrological services and may result in increased wait time and cost to

the system. There was also increase in inappropriate referrals. Fortunately, the time series plot in chapter 3 figure 5 indicates that the number of inappropriate referrals after an initial increase was declining over the year and thus in the coming years, this may be less of a problem, although at this stage it is uncertain whether this trend has continued. Further, incompleteness of referral packages also probably creates inefficiencies in the system. Nevertheless health care systems might want to consider optimization of nephrology services by reducing inappropriate referrals and improving completeness of referral packages. Until this is done, it will be difficult to understand fully the implications of eGFR reporting on health care systems.

#### **4.2 Meaning of the study (Chapter 2): possible mechanisms and implications for clinicians and policy makers “Interventions to improve outpatient referrals from primary care to secondary care”**

Limited data are available to make policy decisions regarding interventions to improve the referral patterns from primary care to secondary care. Dissemination of guidelines with active involvement of secondary care providers is likely to be effective. Structured referral sheet are also likely to be effective but on a population basis it would mean every specialist to have its own referral sheet which would create logistical issues. It remains to be seen if advances in information technology will be helpful in overcoming the logistical issue of structured referral sheets. Passive diffusion of referral guidelines does not seem to be effective. Organizational interventions seem to be promising (our current study

which is not included in the current review also showed positive results of organizational change). The effect of financial interventions on quality of referral is uncertain at present.

## **5.0 Unanswered questions and future research**

### **5.1 Unanswered questions and future research (Chapter 3) “Change in Referral Patterns to Nephrologists after Estimated Glomerular Filtration Rate (eGFR) Reporting: An interrupted time series analysis”**

In order to improve the referral process and make the referral process more efficient for referral to nephrology, studies should be conducted using sound methodological techniques to understand the determinants of inappropriate referrals as well as reasons for referral packages to be incomplete. There is a need to determine the contributions of different entities (professional education, organizational structure and methods of reimbursement for physicians) to explore both the determinants of inappropriate referrals and lack of communication between primary care and nephrologists. Intervention studies of high methodological qualities will then be needed to evaluate the interventions designed from above knowledge to improve the referral process in the field of nephrology. These studies will help in assessing the over all impact on health system demand for nephrological services.

## **5.2 Unanswered questions and future research (Chapter 2) “Interventions to improve outpatient referrals from primary care to secondary care”**

Our review updated the literature till October 2007. It is now about 3 years since our review and studies published regarding eGFR reporting may qualify for inclusion to the systematic review, thus this review now requires to be updated.

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# Appendices

## OAML Communiqué

NOVEMBER 2005

### Routine Reporting of Estimated Glomerular Filtration Rate

Ontario's community laboratories will soon begin reporting an estimated glomerular filtration rate (eGFR) for all adult patients (19 and older) for whom a serum creatinine level is ordered. The eGFR is a calculated value, derived from the Modification of Diet in Renal Disease (MDRD) equation. Laboratories will also continue to report a serum creatinine level with reference ranges.

Ontario's community laboratories will work with the Canadian External Quality Assessment Laboratory (CEQAL) to report a standardized eGFR across all Ontario's community laboratories. This will minimize inter-laboratory variation in reported eGFR's. CEQAL will provide continuing proficiency assessment.

### Background

One in five Canadian seniors now has kidney disease, according to the Kidney Foundation of Canada, and that number is growing by 10 percent per year.

Diabetes is the most common cause of kidney disease in Canada, but kidney disease is also associated with the metabolic syndrome, hypertension and cardiovascular disease. The Kidney Foundation of Canada reports that an estimated 1.9 million Canadians have some form of kidney disease but that most are unaware of it. Early diagnosis and treatment are key to managing kidney disease and to avoiding or, at least, delaying the need for interventions such as dialysis or kidney transplantation.

The eGFR provides practitioners with a measure of renal function that is more sensitive than serum creatinine and thus provides opportunity for earlier detection of kidney disease. Earlier detection permits earlier assessment and management of the disease.

### Why report an eGFR?

- GFR is considered the best index of kidney function but direct measurement is difficult. Indirect estimation of the GFR by established calculation has been demonstrated to be an accurate and efficient replacement for direct measurement, in most situations.
- GFR and creatinine clearance are poorly inferred from serum creatinine alone.
- GFR is inversely and exponentially related to serum creatinine, age, gender and muscle mass.
- If a decreased GFR is reported, physicians must consider a diagnosis of chronic kidney disease (CKD).

### About the MDRD Equation

- The MDRD equation is the most thoroughly validated equation for estimating GFR in individuals with kidney dysfunction.
- Nephrologists routinely use the MDRD equation for estimating GFR.
- The MDRD equation does not require weight as a variable.
- The MDRD equation requires the patient's age, gender and serum or plasma creatinine level.
- The result is normalized to an average adult surface area of  $1.73\text{m}^2$ .
- The MDRD equation should be corrected for race; the eGFR is multiplied by 1.21 to correct for patients of African descent.
- The MDRD equation is not valid in pregnancy.
- An MDRD-calculated eGFR should not be used to adjust drug dosages.
- Further validation of the MDRD equation among other patient groups is underway.
- Patients with diets unusually low in protein or at the extremes of body size should be considered on an individual basis.

Interpretation of Results

The US National Kidney Foundation’s (NKF) diagnostic criteria for stage 1 or 2 CKD are defined as an eGFR greater than 60 mL/min/1.73m<sup>2</sup> and evidence of kidney damage\*. An eGFR < 60 mL/min/1.73m<sup>2</sup> is indicative of CKD even without other criteria and requires further investigation.

Repeat measurements may be helpful in avoiding misdiagnosis of patients with low but stable eGFR. A decrease of 20% in the eGFR should be reviewed for clinical significance.

Stages of Chronic Kidney Disease (National Kidney Foundation, US)

\*Kidney damage is indicated by the presence of significant proteinuria or an elevated urine albumin-to-creatinine ratio.

NKF Stage	Description	eGFR (ml/min/1.73m <sup>2</sup> )
1	Kidney damage with normal or elevated GFR	≥90
2	Kidney damage with mildly depressed GFR	60 - 89
3	Kidney damage with moderately depressed GFR	30 - 59
4	Severely depressed GFR	15 - 29
5	Kidney Failure	< 15

Reference Table for Population Average GFR’s<sup>1</sup>

Age (Years)	Average eGFR (ml/min/1.73m <sup>2</sup> )
20 - 29	116
30 - 39	107
40 - 49	99
50 - 59	93
60 - 69	85
70+	75

Specialist Referrals

Clinical circumstances and patient history should always be considered in addition to laboratory findings; however, it is recommended that referral to a renal specialist be considered when

- The reported/repeated eGFR is less than 30 mL/min/1.73m<sup>2</sup>
- The reported/repeated eGFR has declined by 20% or more
- Significant proteinuria as evidenced by a urine albumin/creatinine ratio >60 is reported.

To Learn More

For additional resources and answers to Frequently Asked Questions: [www.oaml.com/eGFR](http://www.oaml.com/eGFR)

Acknowledgements

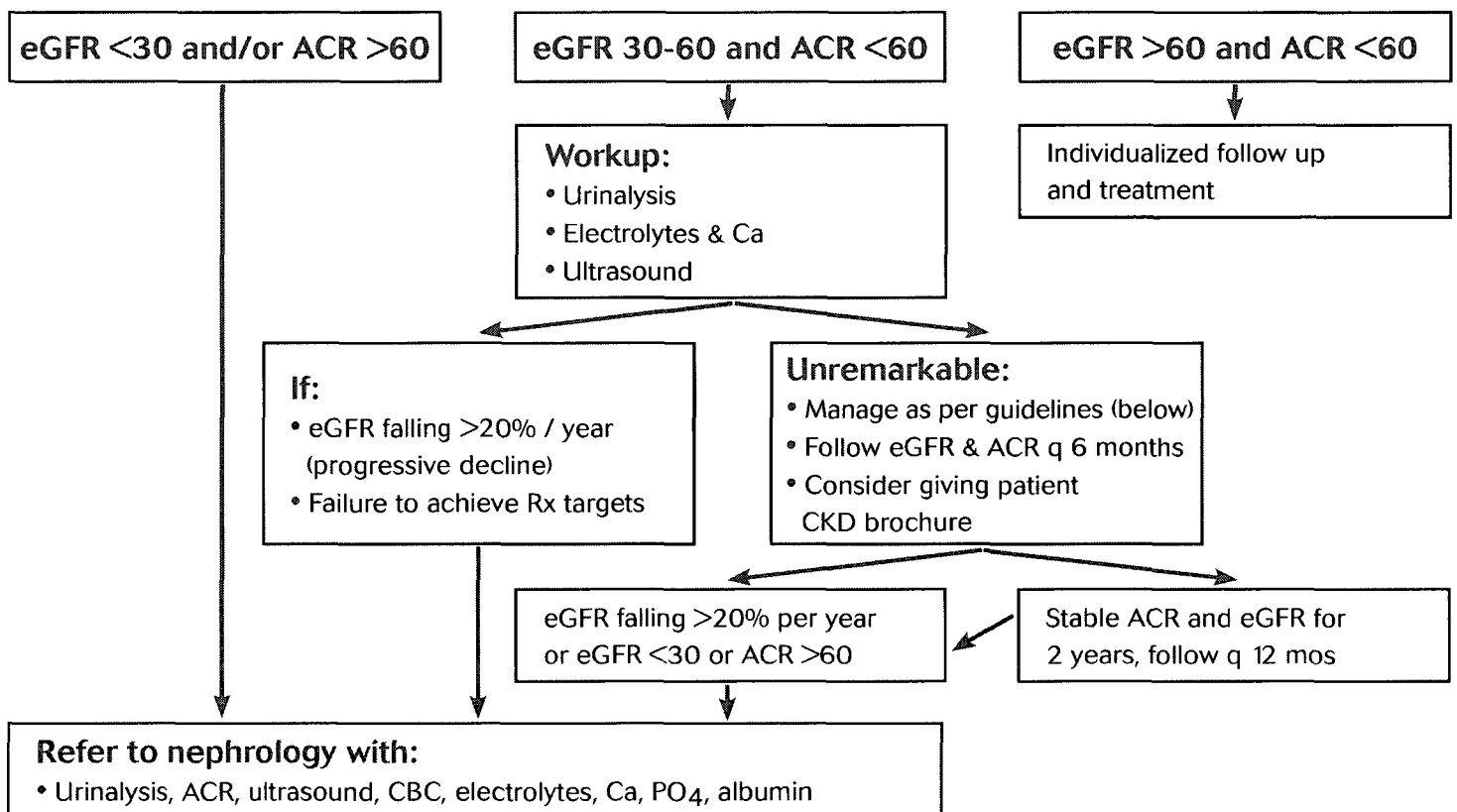
The OAML wishes to acknowledge the contributions of Drs. Ayub Akbari, Robert Bell, Jolanta Karpinski and Peter Magner, Division of Nephrology/Department of Medicine, Kidney Research Centre, University of Ottawa; Christine Collier PhD, FCACB; Sheila Boss PhD, FCACB and Dr. Frank Thompson, MDS Laboratories; Joel Goodman PhD, FCACB, Gamma-Dynacare Laboratories and Mr. John Hamilton.

<sup>1</sup> Coresh, J. “Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third National Health and Nutrition Examination Survey,” *Am J Kidney Dis.* 2003; 41 (1-12).



# Detection, Monitoring & Referral of CKD

- **Identify patients in your practice with elevated risk of CKD:**
  - Patients with hypertension
  - Patients with diabetes mellitus
  - Family hx of end stage (Class V) renal disease  
*(also needs ultrasound of kidneys)*
  - Patients with vascular disease
  - Patients with unexplained anemia
  - Heart failure
  - First Nations Peoples
- **Screen with eGFR and albumin to creatinine ratio in urine (ACR).**
- **If eGFR <60 and/or ACR >60, repeat them in 2-4 weeks. Then if...**



## Implement measures to modify CV risk factors

- Lifestyle modification, smoking cessation
- Treat cholesterol to target as per highest CV risk category
- Consider ASA 81 mg daily
- In diabetics, optimize blood sugar control

## Minimize further kidney injury

- If possible, avoid nephrotoxins such as NSAIDs, aminoglycosides, I/V and intra-arterial contrast etc. (if eGFR <60)
- If contrast is necessary, consider prophylactic measures (if eGFR <60)

## Treatment targets: implement measures to slow rate of CKD progression

- Treat to target BP <130/80
- ACEI and/or ARB are first line therapies in pts with albuminuria or proteinuria (monitor K and Cr or eGFR)
- Target urine albumin/creatinine ratio <40

**Assessment of Referral Patterns to Nephrologists after eGFR reporting**

<b>General Information of the patient</b>		Date of referral: mm/dd/yyyy	Clinic Date: mm/dd/yyyy
Birth: Month / Year		Gender: <input type="checkbox"/> 1 = male <input type="checkbox"/> 0 = female	Nephrologist cancelled appointment: <input type="checkbox"/> 2 = Patient sent to ER <input type="checkbox"/> 1 = yes <input type="checkbox"/> 0 = no
<b>Family Physician</b> <input type="checkbox"/> 1= yes <input type="checkbox"/> 0= no Specialty: <input type="checkbox"/> 0=family physician/GP		MD Family Name:  MD First Name:	Exclusion reason: <input type="checkbox"/> 0 none <input type="checkbox"/> 1 referred by specialist <input type="checkbox"/> 2 repeat referral <input type="checkbox"/> 3 referred by ER <input type="checkbox"/> 4 referred or followed by non Ottawa Hospital Nephrologist <input type="checkbox"/> 5 in-patient referral
Postal code:	City:	Year of graduation:	<b>Case included for data collection</b> <input type="checkbox"/> 1 = yes <input type="checkbox"/> 0 = no
<b><i>If case is included proceed with data collection below.</i></b>			
<b>Reasons for referral listed?</b> <input type="checkbox"/> 1= yes <input type="checkbox"/> 0=no		<input type="checkbox"/> 17 proteinuria	
<b>Reasons for referral (mark all what was given):</b>		<input type="checkbox"/> 18 microalbuminuria	
<input type="checkbox"/> 1 CKD		<input type="checkbox"/> 19 hyperkalemia	
<input type="checkbox"/> 2 Chronic renal failure		<input type="checkbox"/> 20 hypertension	
<input type="checkbox"/> 3 renal insufficiency		<input type="checkbox"/> 21 hematuria	
<input type="checkbox"/> 4 renal/kidney impairment		<input type="checkbox"/> 22 kidney stone	
<input type="checkbox"/> 5 impaired renal/kidney function		<input type="checkbox"/> 23 glomerulonephritis	
<input type="checkbox"/> 6 abnormal renal/kidney function		<input type="checkbox"/> 24 kidney cyst	
<input type="checkbox"/> 7 deteriorating/worsening/declining renal/kidney function/status.		<input type="checkbox"/> 25 single kidney	
<input type="checkbox"/> 8 renal/kidney problem		<input type="checkbox"/> 26 anemia	
<input type="checkbox"/> 9 renal/kidney failure		<input type="checkbox"/> 27 UTI	
<input type="checkbox"/> 10 renal/kidney disease		<input type="checkbox"/> 28 creatinine xxx	
<input type="checkbox"/> 11 rising creatinine		<input type="checkbox"/> 29 eGFR xxx	
<input type="checkbox"/> 12 low eGFR		<input type="checkbox"/> 30 creatinine clearance xxx	
<input type="checkbox"/> 13 low creatinine clearance		<input type="checkbox"/> 31 others: specify:	
<input type="checkbox"/> 14 elevated/ increased creatinine			
<input type="checkbox"/> 15 nephropathy			
<input type="checkbox"/> 16 increasing/elevated urea			
If reasons for referral is not clear. Defer to PI: <input type="checkbox"/> yes <input type="checkbox"/> no		Was there a written statement indicating Family Physician unable to achieve treatment target?  <input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no	

**Section B: Data from Family Physician**

Name of Lab test	Result	Date	Name of Lab	Result	Date	Name of Lab
Serum Creatinine within the last 2 years						
eGFR within the last 2 years						
24 hr Creatinine Clearance with in the last 2 years						

Name of Lab test	Result	Date	Name of Lab
24 hr urine – protein			
Random urine: Albumin & Creatinine Ratio			
Protein			
Creatinine (collect data if protein result is available)			
Albumin			
Phosphate/phosphorus			
Calcium			
Hemoglobin			
Sodium			
Potassium			
Chloride			
HCO3/TCO2			
Urinalysis: <input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no			
Protein			
Blood			
Random glucose			
Fasting glucose			
Kidney U/S report present or ordered	<input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no		
Kidney CT scan report present or ordered	<input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no	Medical condition listed?	<input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no
Kidney MRI report present or ordered	<input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no	Medication listed	<input type="checkbox"/> 1=yes <input type="checkbox"/> 0= no



**Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches**

751 Parkdale Avenue Suite 106, Ottawa, Ontario K1Y 1J7 613-798-5555 ext. 14902 Fax: 613-761-4311  
<http://www.ohri.ca/ohreb>

July 5, 2010

Dr. Ayub Akbari  
Ottawa Hospital - Riverside Campus  
The Centre for Kidney Disease

Dear Dr. Akbari:

**RE: Protocol# - 2005308-01H Assessment of Referral Patterns to Nephrologists**

**Renewal Expiry Date - July 5, 2011**


Thank you for your letter from Judy Cheesman dated June 25, 2010. I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHREB's review and approval.

In the future, please ensure to submit the Annual Renewal Report 30-60 days prior to the date of expiry in order to allow for sufficient time for review of the request without the risk of a lapse in ethical approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

  
Raphael Saginur, M.D.  
Chairman  
Ottawa Hospital Research Ethics Board

/kd

**Table of parameter estimates, deviance statistic and r-squared values for outcome measures.**

$$\text{Full Model } Y_i = \alpha + (\beta_1 T_i) + (\beta_2 P_i) + (\beta_3 T_i P_i) + v_i$$

$$v_i = -\phi_1 v_{i-1} + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \sigma^2)$$

$$\text{Nested Model } Y_i = \alpha + (\beta_2 P_i) + v_i$$

$$v_i = -\phi_1 v_{i-1} + \varepsilon_i$$

$$\varepsilon_i \sim N(0, \sigma^2)$$

$Y_i$  is the response variable at time  $i$ ,  $\alpha$  is the intercept,  $T_i$  is the indicator variable, 0 or 1, 0 = pre-intervention and 1 = post-intervention,  $P_i$  is the time variable of the study (1,2,3.....52).

Outcome Measure		$\alpha$	$\beta_1$	$\beta_2$	$\beta_3$	AIC	$R^2$
Number of appropriate referrals	Full Model	28.5	8.7	-0.25	0.09	351.1	0.22
Number of appropriate referrals	Nested Model			0.12		356.5	0.06
Total number of referrals	Full Model	52.7	36.1	-0.49	-0.33	396.3	0.34
Total number of referrals	Nested Model			0.14		411	0.06
Proportion of appropriate referrals	Full Model	0.5	-0.21	0.00	0.00	-135.6	0.21
Proportion of appropriate referrals	Nested Model			0.00		-131	0.07
Referral Packages Complete for eGFR $\geq$ 30 ml/min/1.73 m <sup>2</sup>	Full Model	2.4	5.1	0.00	-0.09	226	0.21
Referral Packages Complete for eGFR $\geq$ 30 ml/min/1.73 m <sup>2</sup>	Nested Model			0.04		229	0.09
Referral Packages Complete for eGFR $<$ 30 ml/min/1.73 m <sup>2</sup>	Full Model	0.0	0.43	0.0	0.0	-1.3	0.14
Referral Packages Complete for eGFR $<$ 30 ml/min/1.73 m <sup>2</sup>	Nested Model	0.0		0.0		-2.7	0.09