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Synthesizing regulatory guidance for demonstrating preclinical efficacy and translating promising cell therapies to early phase clinical trials: a scoping review

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Abstract

Background Regulatory applications for cell therapy face more objections compared to conventional small molecule or biological drugs, leading to delays in market approval and clinical adoption. Increased regulatory objections frequently relate to issues regarding preclinical evidence, such as experimental design of animal studies, selection of animal models, endpoints, and determination of mechanism of action. Synthesis and clarification of the preclinical evidence necessary to demonstrate treatment efficacy and advance into early-phase clinical trials is needed to help researchers avoid regulatory objections.

Methods We conducted a scoping review in which we searched repositories of the *International Council for Harmonisation* and all national member organizations ($N=38$) for documents related to preclinical studies of cell therapies. Active guidance documents related to cell therapy were included, with no restrictions based on the year or language of publication. Data extraction was conducted in duplicate with conflicts resolved through consensus discussion.

Results From 1215 identified documents, a total of 182 were included and analyzed, with 71% originating from ten major regulatory agencies. The most prevalent preclinical item addressed was the mechanism of action ($n=161$, 88% of documents), underscoring its importance in bridging preclinical findings to clinical application. Most documents ($n=140$, 77%) emphasized the importance of using clinically relevant preclinical models, though specific recommendations on models of disease were less common ($n=81$, 45%). Selection of clinically relevant intervention parameters ($n=136$, 75%) and outcome measures ($n=121$, 66%) were also frequently recommended, but selection of relevant comparator groups appeared less frequently ($n=35$, 19%). Furthermore, robust study design elements such as randomization and blinding were less frequently recommended, appearing in 31% of documents ($n=57$). Comparison with clinical trial guidance revealed a significant gap in the rigor of study design recommendations for preclinical research.

Conclusions Regulatory guidance for preclinical efficacy studies often recommends a strong emphasis on the clinical relevance of animal models, intervention parameters, outcomes, and mechanism of action. Incorporating these

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recommendations into early preclinical studies should improve the acceptability of preclinical evidence for approval by the relevant national regulators and can be used as a guide to ensure that all evidence that regulators say they expect is efficiently assembled into new clinical trial applications.

Keywords Preclinical, Animal, Cell therapy, Stem cell, Clinical trials, International Council for Harmonisation, Regulatory, Guidance, Study design, Best practice

Background

The successful development of "bedside-ready" novel cell therapies represents an enormous challenge (Table 1) [3]. In Europe, > 500 clinical trials of cell and tissue therapies have been conducted since 2009, but only 25 received market authorization, with 7 subsequently withdrawn or suspended [4–6]. Such low rates of success reflect a challenging research and development environment that includes potential struggles or misalignment between researcher, industrial, and regulatory interests throughout the research, development, and market approval process.

Recent studies have demonstrated several areas to improve the translation of cell therapies. Cell therapies experience more objections during regulatory consideration compared to traditional biological therapeutics with similar mechanistic targets [7]. These increased objections are often related to preclinical elements such as the experimental design of animal studies, animal models, endpoints, as well as the determination of the mechanism of action (Table 1) [7, 8]. In the European Union, as with many other jurisdictions, a high proportion of cell therapies are developed either in academic settings or by small to medium-sized enterprises, where conducting fundamental studies to a high level of rigor can be difficult due to limited availability of scientific and/or regulatory resources and expertise compared to large industry [7, 9]. Researchers describe regulatory challenges as the most common issue they face for cell therapies, with navigating country-specific requirements as the most prevalent obstacle [9]. Thus, academic sponsors and small- to medium-sized enterprises could benefit from clarification of international regulatory requirements for the approval of cell therapies to reduce the objections faced during regulatory consideration.

A related concern is determining what constitutes sufficient "proof of concept" of treatment efficacy in preclinical studies before launching early-phase clinical trials [10]. Clinical investigators and product investors both have significant interests in pursuing potential treatments with the greatest likelihood of clinical success. This is reflected in the predominant focus on preclinical treatment efficacy and mechanisms of action in both investigator brochures and non-regulatory guidance documents, such as the *International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation* [2, 11–17]. In contrast, regulatory guidance for preclinical studies is often limited to determination of safety (toxicology, carcinogenicity, etc.), pharmacokinetics/dynamics, and initial dosing,

Table 1 Definitions

Efficacy	The extent to which a specific intervention produces a beneficial result under ideal conditions [1]. Demonstrating efficacy may involve multiple elements, as defined by the *ISSCR Guidelines for Stem Cell Research and Clinical Translation* (sec. 3.3) [2].
Efficacy—mechanism of action	Evidence connecting a cell-based intervention's therapeutic activity to a pathophysiological process related to the disease of interest (e.g., evidence that the intervention interacts with a disease-relevant process of interest).
Efficacy—disease modification	Ability to modify disease or injury when applied in biological systems, and under conditions, that are similar to expected trials (e.g., reduction in size of a tumor by a cancer therapy).
Efficacy—intervention characteristics	Optimal conditions necessary for the health intervention to exert its effect (e.g., evidence of an effective dose, co-intervention, or route of administration).
Efficacy—effect characteristics	Sufficient magnitude or durability of disease modification or injury control to be clinically meaningful (e.g., reduction in mortality at a clinically relevant duration of follow-up).
Preclinical	A phase of research and development using both in vitro and in vivo (often animal) models of disease to evaluate the safety and potential efficacy of novel health interventions. Often precedes human testing.
Cell(ular) therapy	Therapies containing viable cells of allogeneic or autologous origin undergoing a manufacturing process. These cells may be combined with non-cellular components and/or may be genetically modified.
Regulatory guidance	Guidelines and recommendations developed by regulatory authorities to provide a framework for drug development and regulatory review. These documents often focus on the design and conduct of high-quality studies seeking to evaluate the manufacturing quality, safety, and/or efficacy of novel health interventions.

with limited guidance for therapeutic efficacy [18–22]. A comparison of United States Food and Drug Administration (FDA)/European Medicines Agency (EMA) and academic guidance for drug development across a variety of therapeutic areas revealed overlap in only 4% of recommended elements with regard to preclinical treatment efficacy [23]. This discrepancy between regulatory and academic/small-to-medium enterprise priorities may create barriers to efficient advancement of novel cell therapies if the evidence being generated by researchers does not align with regulatory expectations or contains study design features that risk biasing findings to an overestimation of potential treatment benefits.

To clarify regulatory expectations and identify suggested practices for preclinical cell therapy development, we conducted a scoping review to map and synthesize available regulatory guidance on how preclinical treatment efficacy should be demonstrated to support the advancement of cell therapies into clinical trials. We summarized available guidance, enabled evaluation of variation between regulators, and provided a comprehensive list of approaches to establishing preclinical treatment efficacy in international guidance. This information will aid researchers in academic, startup, hospital, and industry organizations with planning appropriate preclinical studies to avoid downstream regulatory objections [7]. Ultimately, this study aims to improve the efficiency of producing and selecting the best cell therapy candidates for further development and maximize the value of the cell therapy research and development pipeline.

Methods

Scoping reviews offer a flexible framework to summarize the breadth and depth of existing literature for a specific field [24]. In this scoping review, we followed best practices from the academic literature and Joanna Briggs Institute (JBI) [24–28]. Following in-principle-acceptance of the Stage 1 protocol by *BMC Medicine* (May 13, 2024), all related documents were registered on Figshare (May 16, 2024; https://doi.org/10.6084/m9.figshare.25836682.v1) and Open Science Framework (May 22, 2024; https://osf.io/c3fxd).

Review question

What types and characteristics of preclinical efficacy evidence do regulatory guidance documents require or recommend for novel cell therapies to be advanced to human clinical trials?

Eligibility criteria

Eligibility criteria were defined according to JBI's Population, Concept, Context framework [28]. Regulatory agency definitions of efficacy, preclinical/nonclinical data, and cellular therapies can vary across countries, which necessitated the use of inclusive operational definitions that captured the scope of the concepts of interest in the present study (Table 1). Regulatory agency classifications of what constitutes a "cell therapy", or if such therapies are distinguished from other classes of drugs/treatments, are particularly varied across regulators. To be inclusive of global recommendations that would apply to cell therapies, we sought to capture regulatory recommendations for preclinical efficacy that would apply to cell therapies, even for countries that do not differentiate cell therapies from other drug classes (e.g., biologicals, small molecules). Specifically, our eligibility criteria were as follows:

- **Population:** regulatory guidance documents from national member organizations of the International Council for Harmonisation (ICH), guidance documents provided directly by the ICH, and other policy document sources ($N = 38$, see "Sources of evidence" below).
- **Concept:** Regulatory guidance documents containing recommended types and/or characteristics of *preclinical efficacy evidence* relating to cellular therapy interventions to be *advanced to human clinical trials or usage* were *included* (Table 1) [2].
- **Context:** Regulatory guidance documents with information relating to the demonstration of preclinical treatment efficacy for any type of cellular therapy were *included*. If an organization did not provide specific guidance for cellular therapies, then guidance relating to any type of biological therapy was *included*. If an organization did not provide specific guidance for cell therapies or biological therapies, then general guidance relating to all types of drug therapeutics was *included*. If an organization provided general guidance related to therapeutics, then national laws relating to drug approval were also *included*. Documents with an indication that they were no longer in active force, or currently used, by the original publishing organization were *excluded*. Guidelines related to preclinical evidence for non-health uses, such as agricultural or environmental applications, were *excluded*. There were no search restrictions based on year or language of publication, but only the most recent version of a given document was used, and all documents were translated to English, using Google Translate or DeepL prior to data extraction. Verification of data extracted from translated articles was performed by those with native proficiency in the original language, where possible.

Sources of evidence

Separate searches for relevant documents were performed on the regulatory guidance document repositories of leading regulatory bodies. See below and Supplementary Material 1, Table S1 for a complete list and search dates of all repositories.

International Council for Harmonisation (ICH)

- All ICH guidelines in Quality, Safety, Efficacy, and Multidisciplinary categories

Regulatory agencies (identified from ICH membership)

Members ($n=15$)

- Brazil—ANVISA: Brazilian Health Regulatory Agency
- Canada—Health Canada
- China—NMPA: National Medical Products Administration
- Chinese Taipei (Taiwan)—TFDA: Taiwan Food and Drug Administration
- Egypt—EDA: Egyptian Drug Authority
- European Union—EMA: European Medicines Agency / European Commission
- Japan—PMDA: Pharmaceuticals and Medical Devices Agency / MHLW: Ministry of Health, Labour, and Welfare
- Mexico—COFEPRIS: Federal Commission for the Protection against Sanitary Risks
- Republic of Korea—MFDS: Ministry of Food and Drug Safety
- Saudi Arabia—SFDA: Saudi Food and Drug Authority
- Singapore—HSA: Health Sciences Authority
- Switzerland—Swissmedic
- Turkey—TITCK: Turkish Medicines and Medical Devices Agency
- United Kingdom—MHRA: Medicines and Healthcare Products Regulatory Agency
- United States of America—FDA: Food and Drug Administration

Observers ($n=22$)

- Algeria—ANPP: National Agency of Pharmaceutical Products
- Argentina—ANMAT: National Administration of Drugs, Food, and Medical Devices
- Armenia—SCDMTE: Scientific Center of Drug and Medical Technology Expertise
- Australia—TGA: Therapeutic Goods Administration
- Azerbaijan—AEC: Analytical Expertise Center
- Colombia—INVIMA: National Institute for Food and Drug Surveillance
- Cuba—CECMED: Center for State Control of Drugs, Equipment, and Medical Devices
- Hong Kong, China—PPBHK: Pharmacy and Poisons Board of Hong Kong
- India—CDSCO: Central Drugs Standard Control Organization
- Indonesia—FDA: Indonesian Food and Drug Administration
- Iran—IFDA: Iran Food and Drug Administration
- Israel—CPED: Ministry of Health, Pharmacy Division
- Jordan—JFDA: Jordan Food and Drug Administration
- Kazakhstan—NDDA: National Center for Expertise of Medicines and Medical Devices
- Lebanon—MOPH: Ministry of Public Health
- Malaysia—NPRA: National Pharmaceutical Regulatory Agency
- Moldova—MMDA: Medicines and Medical Devices Agency
- Nigeria—NAFDAC: National Agency for Food and Drug Administration and Control
- Russia—Roszdravnadzor: Federal Service for Surveillance in Healthcare
- South Africa—SAHPRA: South African Health Products Regulatory Authority
- Tunisia—DPM: Directorate of Pharmacy and Medicine
- Ukraine—SECMOH: State Expert Center of the Ministry of Health

Government policy documents

- NIH ClinRegs, an international database of regulatory information related to clinical trials, stratified by country [29].

Internally referenced documents

- Any legislative or guidance documents internally referenced within included documents discussed in a context relevant to the determination of preclinical treatment efficacy (see "Screening and data charting" below) were obtained for screening (secondary

sources). Further references from within these secondary sources were not obtained for screening.

Search strategy

Given that the target regulatory guidance documents were not readily accessible from traditional indexed academic sources (e.g., PubMed, Embase, etc.), we searched the websites of each regulatory agency identified above to locate documents. An information specialist (Risa Shorr, MLS) provided guidance on identification of relevant databases and search terms. The specific strategy for searching each website broadly consisted of (1) locating cell therapy-specific document collections curated by each agency, (2) using search filters and keyword searching in site-specific databases for each agency, and (3) contacting each agency to request documents.

Search terms applied were as follows, with the intention to capture all regulatory guidance documents related to therapies containing viable cells of allogeneic or autologous origin undergoing a manufacturing process. These cells may be combined with non-cellular components and/or may be genetically modified (Table 1):

- Cell OR cellular OR cell-based OR stem OR gene-modified cell OR advanced;
- Preclinical OR nonclinical OR animal OR in vitro OR in vivo OR in silico;
- Therapy OR therapeutic OR intervention OR treatment OR technology OR medicine;
- Criteria OR requirement OR guideline OR guidance OR regulation OR "regulatory guideline" OR "guidance document" OR "guidance for industry" OR policy OR "position paper"

(1) Official agency websites were searched using the search terms above to identify document collections or webpages containing links related to scientific guidance for cell therapies. Links to these collections were documented. Document collections identified during pilot searching are provided in Supplementary Material 1, Table S1.

(2) Built-in search filters containing any of the search terms above were applied to limit the number of documents identified in agency-specific document repositories (Supplementary Material 1, Table S1), where possible. Keyword searching using the search terms was also performed and relevant documents were imported to DistillerSR (Evidence Partners, Ottawa, Canada) for screening.

(3) Email addresses and links to contact webforms related to regulatory guidance documents for cell therapies, biologicals, general therapeutics, or national laws for drug approval were identified according to the "Eligibility criteria" workflow detailed above. This contact information was identified from each agency's respective regulatory guidance or website if no contact information was provided within the documents. Contact information identified during pilot searching is provided in Supplementary Material 1, Table S1 and was used to request additional documents from each organization.

Screening and data charting

Documents identified from each source were uploaded to DistillerSR (Evidence Partners, Ottawa, Canada) to facilitate duplicate identification, screening, and data extraction. Screening and data extraction were performed in duplicate by independent reviewers, with conflicts resolved through further discussion. Pilot data extraction forms were created in DistillerSR through discussion between the investigators using a sample of six example documents identified from Health Canada, FDA, and EMA [21, 22, 30–33]. Generation of data extraction forms using these pilot documents was intended to ensure that all data elements were clearly defined, feasible to extract, and reproducible, and the finalized version was reviewed and agreed on by all investigators. Recalibration and discussion of data extraction forms proceeded iteratively to ensure that any critical elements that were not identified a priori were included. The data extraction forms derived from the pilot items are outlined below and detailed in Supplementary Material 1, Appendix 1.

Document characteristics

Extracted document characteristics included: document title, year of publication, document type/status/scope, publishing organization, contact information, and language of original publication.

Recommended types and/or characteristics of preclinical efficacy evidence for preclinical therapeutics to be advanced to human clinical trials or usage

ICH guidance document E2C(R2) broadly defines efficacy as any "evidence on benefit" derived from both "clinical trials and everyday medical practice" [34]. We aligned our definition of efficacy to the *ISSCR Guidelines for Stem Cell Research and Clinical Translation* (Table 1), as this document provides more specific categories of evidence related to efficacy that are directly relevant

to cell therapies while also capturing the broader ICH E2C(R2) definition accepted by the regulatory agencies included in this study [2]. Discrete text referring to any type of data, study type, or quality recommended to support the preclinical efficacy of cell therapies was noted for each guidance document, which included topics such as:

- Preferred terminology to describe preclinical model and efficacy-related concepts *(e.g., preclinical, nonclinical, efficacy, proof of concept, potential benefit,* etc.*)*
- Relevance of preclinical models to clinical disease *(e.g., recommendations for alignment of ages, comorbidities, disease progression,* etc.*)*
- Mechanism of action *(e.g., forms of evidence connecting an intervention's therapeutic activity to a pathophysiological process)*
- Disease modification *(e.g., forms of evidence that an intervention can modify disease or injury in biological systems)*
- Intervention/comparator characteristics *(e.g., optimal conditions or testing parameters to identify that an intervention has an effect)*
- Effect/outcome characteristics *(e.g., parameters for demonstrating sufficient magnitude, durability, or specific nature of disease modification)*
- Study characteristics *(e.g., recommended methods for design, conduct, or analysis of experiments to determine preclinical treatment efficacy)*

Other preclinical considerations for regulatory approval (not directly related to treatment efficacy)

Other categories of regulatory recommendations or requirements (not related to treatment efficacy) for preclinical studies to be advanced to early-phase clinical trials were noted, as these topics are inextricably linked with efficacy, and pilot searches identified that preclinical efficacy-related information was often bundled in documents with other types of recommendations. This included quality/manufacturing standards, safety, environmental impact studies, ethical considerations, and clinical trial guidance (Supplementary Material 1, Appendix 1).

References relevant to preclinical determination of treatment efficacy

We identified and screened references to documents that were provided in a context directly relevant to recommended types and/or characteristics of preclinical efficacy evidence for cell therapies to be advanced to human clinical trials or usage. This was defined by the data extraction items above *(e.g., mechanism of action, disease modification,* etc.*)* for all primary sources.

Clinical trial recommendations for efficacy

Clinical trial recommendations in ICH guidance document E8(R1), *General Considerations for Clinical Studies* [18], *ISSCR Guidelines for Stem Cell Research and Clinical Translation* [2], and *Good Clinical Trials Collaborative Guidance* [35] were extracted using the same extraction forms used for preclinical studies. This was to enable direct comparison between clinical and preclinical recommendations regarding treatment efficacy. This contrast was used to highlight the current role that efficacy data plays in the drug approval process and how expectations for evidence at the preclinical phase differ from those for market approval.

Data analysis and presentation

Synthesis of the extracted data was descriptive. We compiled comprehensive lists of all evidence types and study characteristics related to the data extraction items. Pilot results were extracted from the documents used to generate and refine the data extraction forms (Supplementary Material 1, Appendix 2). Frequency ranking was performed to highlight the most prevalent recommendations, with the primary set of tables presenting data for both the number and percentage of total *documents* providing each recommendation, as well as the number and percentage of total *regulatory organizations* providing each recommendation. Stratification of recommendations by each regulatory organization was also performed (see Supplementary Material 2). Similarities and inconsistencies across agencies were highlighted when possible. Preclinical recommendations were compared against clinical trial recommendations in the documents described above.

Modifications to the original protocol

As per scoping review best practices, the research team met throughout the screening process to discuss if any modifications to the search strategy, inclusion, or exclusion criteria were required [24]. Documents from the European Parliament ($n=5$) and European Commission ($n=1$) were included as part of the European Union/EMA. Documents from the Japanese Ministry of Health, Labour, and Welfare ($n=1$) were included as part of Japan / PMDA. Documents from the Eurasian Economic Commission Council ($n=2$) were included as part of Kazakhstan/NDDA. Documents from the Association of Southeast Asian Nations Secretariat ($n=1$) were included as part of Malaysia/NPRA. Groupings were determined by the agency website where the documents

were originally identified and correspondence with each agency during searching. ICH E8(R1) was selected as the most relevant guidance for contrasting clinical and preclinical study recommendations based on discussions among the investigative team [18]. This comparison of preclinical and clinical study recommendations was supplemented by the addition of the *ISSCR Guidelines for Stem Cell Research and Clinical Translation* (pre-specified a priori, [2]) and the newly emerging *Guidance for good randomized clinical trials* from the Good Clinical Trials Collaborative (GCTC) [35].

Results

Document characteristics

With 182 meeting eligibility criteria, 1215 documents were identified (Fig. 1). The numbers of documents included for each agency at each level of screening are provided in Supplementary Material 2, Table S2. Overall, 71% ($n=130$) of

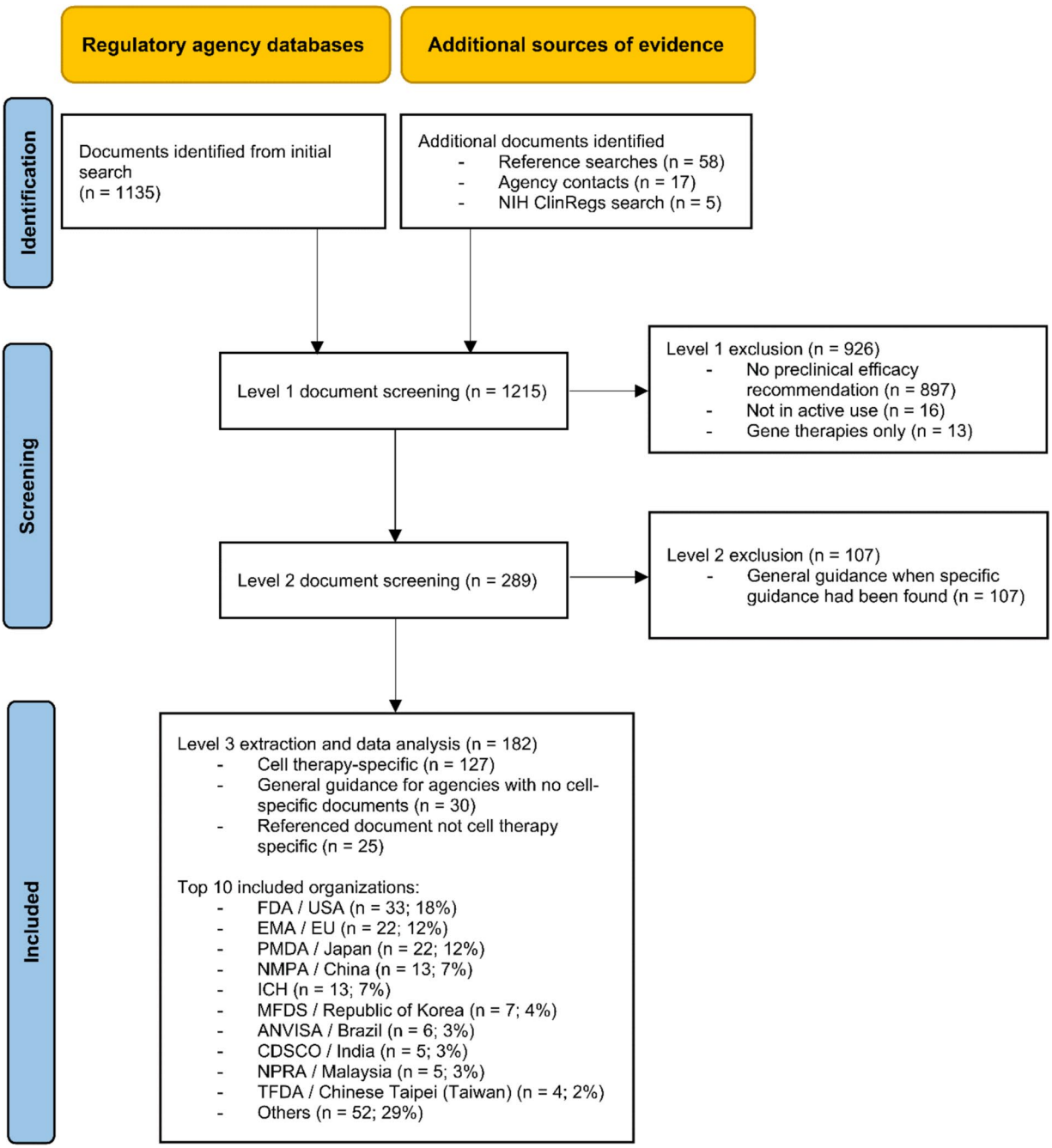

Fig. 1 PRISMA flow diagram

Table 2 Characteristics of included documents

Document characteristic	Frequency ($n=182$)	Percentage of documents (%)
Year of publication		
2021–Present	56	31%
2016–2020	45	25%
2011–2015	35	19%
2006–2010	24	13%
2001–2005	6	3%
1996–2000	4	2%
1991–1995	3	2%
Date not specified	9	5%
Language of original document		
English	105	58%
Japanese	22	12%
Chinese (simplified)	13	7%
Korean	7	4%
Russian	7	4%
Spanish	7	4%
Portuguese	6	3%
Chinese (traditional)	4	2%
Romanian	3	2%
French	2	1%
Ukrainian	2	1%
Arabic	1	< 1%
Farsi	1	< 1%
Indonesian	1	< 1%
Turkish	1	< 1%
Therapeutic area		
General guidance	157	86%
Cancer	7	4%
Cartilage repair	6	3%
Cardiac	3	2%
Cirrhosis	1	< 1%
COVID-19	1	< 1%
Hemophilia	1	< 1%
Neurodegenerative diseases	1	< 1%
Rare diseases	1	< 1%
Retinal disorders	1	< 1%
Skin regeneration	1	< 1%
Spinal cord injury	1	< 1%
Type 1 diabetes	1	< 1%
Cell type		
General guidance	122	67%
Stem cells, unspecified	15	8%
Genetically modified cells, unspecified	11	6%
Human cells, unspecified	8	4%
Induced pluripotent stem cells (iPSC)	5	3%
Xenogeneic cells, unspecified	5	3%
Chondrocytes	3	2%
Somatic stem cells	3	2%
Mesenchymal stem cells	2	1%
Retinal pigment epithelial cells	2	1%
Chimeric antigen receptor (CAR) T cells	1	< 1%
Corneal endothelial cells	1	< 1%
Dendritic cells	1	< 1%
Embryonic stem cells	1	< 1%
Epidermal cells	1	< 1%
Immune cells, unspecified	1	< 1%
Pancreatic islet cells	1	< 1%
Periodontal tissue	1	< 1%
Peripheral blood mononuclear CD34 + cells	1	< 1%

included documents originated from one of ten organizations (Fig. 1; FDA/USA; EMA/EU; PMDA/Japan; NMPA/China; ICH/international; MFDS/South Korea; ANVISA/Brazil; CDSCO/India; NPRA/Malaysia; TFDA/Chinese Taipei (Taiwan)). These regulators with the largest number of guidance documents also tended to provide the broadest recommendations, with more detailed suggestions on approaches to fulfilling the recommendations (described below and in supplementary materials).

Availability of regulatory guidance for demonstrating preclinical efficacy in cell therapies increased over time (Table 2. The first document was published in 1993, 13 documents (7% of the sample) were published prior to 2005, 104 documents (57% of the sample) were published from 2006 to 2020, and 56 documents (31% of the sample) were published from 2021 to the search date (June 27–28, 2024). More than half of the included documents were published in English (58%). A minority (14%) of documents were specific to certain therapeutic areas, with cancer, cartilage repair, and cardiac injury being the most prevalent; 33% of documents provided guidance for specific cell types (Table 2). Supplementary results and tables related to preferred terminology to describe preclinical model and efficacy-related concepts, non-efficacy considerations, and references relevant to preclinical determination of treatment efficacy are discussed in Supplementary Material 2, Appendix 3, Tables S3-S7.

Considerations for evidence of preclinical treatment efficacy to support advancement of cell therapy interventions to human clinical trials

Relevance of preclinical models to clinical population and disease

The majority of documents ($n=140/182$, 77%) and regulators ($n=32/38$, 84%) provided recommendations to ensure that preclinical models were "clinically relevant" to the clinical populations and indications they were

Table 3 Considerations for the selection of clinically relevant animal and disease models

Model characteristics	Documents with at least one recommendation ($n=182$)		Regulators with at least one recommendation ($n=38$)	
Animal model recommendations				
General—"clinical relevance" of model system	140	77%	32	84%
Outline limitations/similarities/differences from humans	84	46%	28	74%
Feasibility of delivering human intervention (anatomic site accessibility, absolute dose size, immunogenicity)	79	43%	20	53%
Physiologic similarity—intervention response (pharmacological response to intervention (PK/PD, ADME))	70	38%	22	58%
Population similarity—demographic considerations (age, sex, weight, health status, physical environment)	46	25%	18	47%
Physiologic similarity—host tissues (target expression, distribution, structure)	42	23%	12	32%
Physiologic similarity—response to disease (Animal susceptibility to human disease under study)	11	6%	8	21%
Population similarity—comorbidities/concomitant medications	6	3%	6	16%
Population similarity—special populations (pediatric, geriatric, pregnant, lactating, menopausal)	2	1%	2	5%
Disease model recommendations				
General—"clinical relevance" of disease model	81	45%	17	45%
Similar disease pathophysiology (implicated pathways, disease definitions, diagnosis criteria)	30	16%	13	34%
Similar manifestation of disease outcomes	16	9%	10	26%
Similar agent used to trigger disease (virus, pathogen, endogenous process)	9	5%	8	21%
Similar time course of disease progression	3	2%	2	5%
Similar time to disease onset (following trigger)	1	< 1%	1	3%
Similar trigger to initiate intervention (clinical sign/criteria)	1	< 1%	1	3%

intended to represent. Specific recommendations are listed in Table 3. Overall, when selecting relevant preclinical models, researchers should be transparent about the similarities and differences of their models from humans and aim to capture characteristics of the downstream human clinical trial population as closely as possible in relation to features such as anatomy, physiology, and population demographics (e.g., age, sex, weight, health status; Table 3).

Recommendations related to the use of clinically relevant *models of disease* were commonly observed across documents ($n=81$, 45%) and regulators ($n=17$, 45%; Table 3). Documents specific to cell therapies recommended utilizing models of disease in preclinical studies more often than documents that were not cell therapy specific (57% vs. 16% respectively; Table S10), highlighting the particular importance of demonstrating preclinical efficacy of cell therapies under relevant disease conditions. Generally, preclinical models of disease should emulate the pathophysiology, progression, and outcomes of the human disease as closely as possible (Table 3).

Mechanism of action

Demonstrating preclinical evidence for the mechanism of action of a cell therapy was the most common recommendation across documents ($n=161$, 88%) and regulators ($n=34$, 89%; Table 4). More specific regulatory considerations for the mechanism of action were provided in approximately 59% of documents and by 75% of regulators. Namely, preclinical evidence should demonstrate that the cell therapy is present in the clinically relevant site of the body, the cell therapy should display functional properties proposed to be relevant to its clinical effect (e.g., presence of relevant cellular phenotype, production of relevant proteins, etc.), and the tissues of the treated individual should demonstrate a pharmacological response in the presence of the cell therapy in line with the proposed clinical effect (Table 4).

Intervention and comparator characteristics

Most documents ($n=136$, 75%) and regulatory agencies ($n=35$, 92%) provided recommendations relating to the use of clinically relevant intervention parameters in preclinical efficacy studies. A lower proportion

Table 4 Considerations for evidence of preclinical treatment efficacy to support advancement of intervention to human clinical trials

Evidence characteristics	Documents with at least one recommendation ($n=182$)		Regulators with at least one recommendation ($n=38$)	
Mechanism of action recommendations				
General—"mechanism of action" should be demonstrated	161	88%	34	89%
Functional properties of intervention (desired chemical/biological expression)	108	59%	29	76%
Localization of intervention (exposure at the target site of action over the desired period)	108	59%	28	74%
Target modulation of host tissues (desired downstream pharmacological activity)	106	58%	28	74%
Intervention recommendations				
General—"clinical relevance" of intervention parameters	136	75%	35	92%
Dosing parameters—dose selection (identification of clinical starting dose)	109	60%	29	76%
Route of administration	106	58%	31	82%
Use of similar intervention product in preclinical-clinical studies	85	47%	26	68%
Dosing parameters—dosing schedules (timing of first administration, interval between doses)	63	35%	26	68%
Dosing parameters—dose range (minimum/maximum dose for biological or therapeutic activity)	57	31%	19	50%
Dosing parameters—dose–response (establishment of biological gradient)	44	24%	18	47%
Co-interventions	24	13%	14	37%
Verification of successful administration/treatment compliance	6	3%	4	11%
Comparator recommendations				
General—"clinical relevance" of comparator parameters	35	19%	15	39%
Comparator—active comparator	13	7%	10	26%
Comparator—placebo-control	13	7%	7	18%
Comparator—concurrent	6	3%	3	8%
Dosing parameters	2	1%	2	5%
Comparator—cross-over	1	< 1%	1	3%
Co-interventions	1	< 1%	1	3%
Route of administration	1	< 1%	1	3%
Verification of successful administration/treatment compliance	1	< 1%	1	3%
Verification that comparator follows the natural course of disease	1	< 1%	1	3%
Effect/outcome recommendations				
General—"clinical relevance" of outcomes	121	66%	30	79%
Surrogate endpoints (biomarkers, imaging, physiological measures)	79	43%	20	53%
Duration of effects/stability of effect	74	40%	23	61%
Minimum validity/reliability criteria for outcomes (accuracy/precision standards)	57	31%	20	53%
Functional endpoints (clinically related task, mechanical tissue properties)	30	16%	10	26%
Time to onset of treatment effect	17	9%	11	29%
Clinical endpoints (disease-related mortality)	12	7%	6	16%
Magnitude/intensity of effects	10	5%	7	18%

of documents ($n=35$, 19%) and regulators ($n=15$, 39%) discussed the need for relevant comparator groups (Table 4). For interventions, the most prevalent recommendations were to use preclinical studies to select a safe and potentially effective starting dose for clinical trials (60% of documents, 76% of regulators). The clinical trial starting dose should be established under preclinical study conditions that emulate the downstream clinical trial, such as by using the same dosing schedule and route of administration (Table 4). Additionally, the cell therapy product used in preclinical studies should be the same, or as similar as possible, to the product that will be used in clinical trials (47% of documents, 68% of regulators). The use of both active comparators (7% of documents, 26% of regulators) and placebo controls (which also encompassed vehicle groups, sham treatments, etc.; 7% of documents, 18% of regulators) were the most frequently observed details when comparator-related recommendations were provided (Table 4).

Effect and/or outcome characteristics

The importance of using clinically relevant outcome measures to assess preclinical efficacy was discussed by most included documents ($n=121$, 66%) and regulatory agencies ($n=30$, 79%; Table 4). Surrogate endpoints (e.g., biomarkers, imaging, physiological measures, etc.; mentioned by 43% of documents, 53% of regulators) were the most recommended type of outcome, especially in the context of trying to establish potential surrogate endpoints in preclinical efficacy studies for use in subsequent clinical trials. Functional endpoints (e.g., clinically related tasks, mechanical tissue properties, etc.; 16% of documents, 26% of regulators) and clinical endpoints (e.g., disease-related mortality, etc.; 7% of documents, 16% of regulators; Table 4) were recommended less frequently, usually in documents that discussed a particular therapeutic area or cell type where more specific clinically relevant recommendations for outcomes could be provided. Other frequent recommendations were to assess that the duration of observed preclinical effects (and persistence of cell therapies in vivo) are relevant to the proposed clinical indication or likely clinical follow-up period in subsequent human trials (40% of documents, 61% of regulators), and that outcome measures have established validity or reliability criteria (31% or documents, 53% of regulators; Table 4).

Study design, conduct, analysis, and reporting

Recommendations related to the design, conduct, and analysis of preclinical efficacy studies were the least frequently observed category among included documents ($n=57$, 31%) and regulatory agencies ($n=25$, 66%; Table 5). Where more details were provided, demonstrating preclinical efficacy under multiple conditions or animal species/models was the most common recommendation (23% of documents, 45% of regulators). Ensuring that an "appropriate" or "sufficient" number of animals were used to demonstrate efficacy was the next most common recommendation (10% of documents, 34% of regulators), but details on how to ascertain an appropriate sample size were not provided. Recommendations related to preclinical study reporting were provided by 42% of documents and 74% of regulators (Table 5). These recommendations were provided in the context of data that should be reported to the regulator, rather than in academic publications. Across regulators, ICH guidance documents M4E and M4S (Common Technical Document format) were recommended as the relevant regulatory reporting standards for data related to preclinical efficacy. One exception to these trends was that the *ISSCR Guidelines for Stem Cell Research and Clinical Translation* also recommended several practices that were not observed in the regulatory guidance, such as

Table 5 Considerations for design, conduct, and analysis of preclinical efficacy experiments

Study characteristics	Documents with at least one recommendation ($n=182$)		Regulators with at least one recommendation ($n=38$)	
Design recommendations				
General—"appropriate" or "best-practices" for design/analysis	57	31%	25	66%
Replication—multiple conditions/models/demographics	41	23%	17	45%
Statistical power/sample size calculation	19	10%	13	34%
Data quality and integrity/study management	16	9%	7	18%
Statistical analysis plan (pre-specified, appropriate)	15	8%	11	29%
Protocol pre-specification/study registration	11	6%	5	13%
Randomization	8	4%	4	11%
Baseline characterization of groups (pre-treatment)	6	3%	4	11%
Blinding	5	3%	2	5%
Replication—independent laboratories	4	2%	3	8%
Replication—within laboratory	3	2%	3	8%
Eligibility criteria (pre-specified)	3	2%	3	8%
Specific study type—confirmatory	2	1%	1	3%
Reporting recommendations				
Reporting/publication requirements for study data (public/required regulatory reporting items)	76	42%	28	74%
Use of reporting standards/guidelines (e.g., ARRIVE or regulatory)	33	18%	17	45%
Deposit/archiving of study materials (code, data, biological samples; either public or with regulator)	21	12%	9	24%
Systematic review/synthesis of existing evidence for treatment	1	< 1%	0	0%

distinguishing between exploratory and confirmatory preclinical studies (and only using confirmatory studies to support claims of clinical utility), synthesizing preclinical evidence using systematic review and meta-analysis techniques, and using relevant academic guidelines for comprehensive reporting of preclinical studies (such as ARRIVE, [36]; Table S17-18).

Data stratified by individual regulatory organization

In addition to the combined proportion of documents and proportion of regulators providing each of the recommendations above in Tables 3, 4 and 5, the recommendations specific to each regulatory organization are provided in Supplementary Material 2. Please see Tables S8-10 for regulator-specific recommendations related to animal selection/models of disease, Tables S11-15 for mechanisms of action, intervention/comparator/outcome selection, and Tables S16-18 for study design, conduct, and reporting.

Comparison with recommendations for trials of human clinical efficacy

Overall, clinical guidance contained many analogous recommendations to those that were also commonly observed in preclinical guidance. This included recommendations to select trial eligibility criteria that are inclusive of clinically relevant populations based on demographic and physiological characteristics, to use clinically relevant intervention parameters and outcome measures, and to report data to regulators using the ICH M4, Common Technical Document format (Supplementary Material 2, Table S19). Clinical guidance also provided a heavy emphasis on the need for appropriate study characteristics to minimize the risk of bias in effect estimates, such as through the selection of appropriate comparator groups, ensuring sufficient sample size, protocol pre-specification/study registration, randomization, and blinding (Table S19); all of which were not frequently observed in the preclinical guidance (Tables 4 and 5). Additionally, several best practices for clinical efficacy trials, such as community/patient partnership throughout protocol development to ensure clinical relevance, pre-specification of primary outcomes, and robust statistical analysis planning (i.e., use of intention-to-treat analysis, trial-stopping rules, handling of multiple comparisons, etc.) were prominent areas of clinical trial guidance, but absent from preclinical study recommendations (Table S19).

Discussion

Summary and implications of results

We identified and synthesized recommendations from 182 regulatory documents that provide guidance on preclinical efficacy studies of cell therapies, representing 38 major regulatory bodies. This synthesis offers a comprehensive resource for designing studies that align with regulatory expectations and aims to streamline successful transition into clinical trials. We identified several key recommendations that were commonly found across most regulatory organizations:

1) Optimize selection of clinically relevant preclinical models through close emulation of the clinical population and disease that models are intended to represent (including alignment with human anatomy, physiology, demographics, and disease pathophysiology);
2) Administer interventions using parameters that match the conditions in anticipated clinical trials (including the dosage, administration route, treatment schedule, and using as similar of an intervention product as possible to the actual clinical product);
3) Use outcome measures that are meaningful for clinical translation (including surrogate endpoints and biomarkers that could also be deployed in clinical trials) and ensure that the duration of observed effects and persistence of therapy match the clinical indication;
4) Demonstrate potential mechanisms of action (including localization of the therapy to the intended site of action, functional cellular properties that align with expected clinical effects, and induction of a pharmacological response in host tissues);

Additionally, the *ISSCR Guidelines for Stem Cell Research and Clinical Translation* and clinical regulatory efficacy guidance documents recommend practices to minimize study bias (e.g., randomization, blinding) that researchers could use to supplement preclinical regulatory guidance with best practices to ensure robust and valid study designs.

The list of recommendations we identified can be used by a variety of parties involved in the development and regulation of cell therapies. For example, both academic preclinical researchers and industry cell therapy developers, regardless of home country, should consider implementing the recommendations we identified into preclinical study designs to enhance the likelihood of regulatory acceptance and translation of their data into clinical settings. This will ensure that preclinical data is broadly applicable across all ICH member countries. Clinical researchers or research ethics boards involved in planning early-phase clinical trials of cell therapies can utilize the recommendations as a guide for assessing the completeness of supporting preclinical

evidence prior to trial initiation. Regulatory agencies seeking to harmonize their guidance with other organizations can use this information to prompt a dialogue within and across agencies on recommendations that could potentially be updated or expanded in the future. Finally, funding bodies and policymakers might use this review to guide the allocation of resources, ensuring that funded preclinical studies incorporate both clinically relevant parameters and methodological rigor. By integrating the recommendations synthesized in this review, parties involved in cell therapy development can contribute to the more effective and efficient translation of cell therapies from preclinical research to clinical application.

Guidance from non-regulatory sources

In the broader literature, the *ISSCR Guidelines for Stem Cell Research and Clinical Translation* offers a prominent and directly relevant preclinical guidance documents for cell therapy developers [2]. This document is referenced by a number of regulatory agencies that provide limited cell therapy guidance of their own. It highlights similar preclinical recommendations as the regulatory guidance that we extracted in the present study, placing a consistent emphasis on designing preclinical studies that are clinically relevant and aligned to real-world settings. However, the *ISSCR Guidelines* further emphasize study design characteristics that help reduce bias and improve preclinical study validity, such as sample size calculation, use of appropriate controls, randomization, and blinding, that were rarely observed in regulatory guidance.

Similarly, several systematic reviews of academic guidance for preclinical biomedical studies (not cell therapy specific) also emphasize the importance of design factors that reduce bias [12, 37]. For example, while 89% of academic guidelines recommend sample size calculations [12], it was included in only 10% of regulatory guidelines in our sample. Recommendations for randomization (77% vs. 4%) and blinding (77% vs. 3%) show similar discrepancies [12]. Both regulatory and academic guidance provide a strong foundation for the preclinical development of effective cell therapies with their recommendations to strive for clinically relevant study parameters wherever possible; however, preclinical researchers can maximize the robustness of preclinical evidence and further support successful clinical translation by also incorporating rigorous design practices, such as randomization and blinding, into their studies [12, 37].

Limitations

This review has limitations. Documents were identified from a large variety of regulatory websites and document sources, which had varied functionality for searching and were available in multiple languages. We utilized native language speakers to help identify the most appropriate document sources and searched all websites in duplicate to ensure a comprehensive search, but it is possible that relevant documents could have been missed. Secondly, the complex layout, expansive scope (some documents were hundreds of pages), inconsistent use of terminology across regulatory documents, and the fact that many documents were translated into English means that some recommendations may have been overlooked. We utilized duplicate reviewers and native language speakers to verify that data extracted from translated documents matched the original intent, where possible, but it is possible that some nuances may not have been fully captured.

Conclusions

This scoping review provides a comprehensive synthesis of regulatory guidance for preclinical efficacy studies of cell therapies across all ICH member countries. Incorporating these elements into planned preclinical studies during early product development will promote efficient translation into clinical trials, improve the acceptability of preclinical evidence by national regulators, and enhance the robustness of preclinical findings. Continued dialogue and collaboration between regulatory bodies, researchers, and clinicians will be essential to further advancement of optimal strategies for the preclinical development phase of cell therapies, particularly regarding practices to minimize risk of bias, which are foundational principles of clinical efficacy studies.

Supplementary Information

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Supplementary Material 1. Supplementary methods and pilot materials.

Supplementary Material 2. Supplementary data.

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Authors' contributions

MSJ, JK, PB, DIM, MML, and DAF contributed to the conception and design of the study. MSJ, CX, RB, and HW acquired and analyzed the data. MSJ, MML, and DAF drafted the initial version of the Stage 1 protocol. All authors contributed to revisions of the Stage 1 protocol, preparation of the Stage 2 manuscript, and approved the submitted version.

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Data availability
The protocol and datasets generated and/or analyzed during the current study will be made publicly available on the Open Science Framework (https://osf.io/c3fxd) upon publication of the final report.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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