3D Printing in Medicine

METHODOLOGY

Open Access

Assessing the landscape of clinical and observational trials involving bioprinting: a scoping review

Yumi Briones[1,2*], Beatrice Pascua[1,3], Narra Tiangco[1,4], Isabel Crisostomo[1,5†], Samantha Casiguran[1†] and Roland Remenyi[1*]

Abstract

Objective Bioprinting is a tissue engineering technique that is rapidly evolving to include complex clinical applications. However, there is limited evidence describing how far bioprinting has progressed past the pre-clinical stage. Thus, we conducted a scoping review to assess the landscape of clinical studies, including interventional and observational trials, involving bioprinting by charting trends in general characteristics, bioprinting application, and trial design.

Methods The term "bioprint" and its variants were searched in five trial databases (ICTRP, ScanMedicine, CENTRAL, NIHCC, HCCTD) and two registries (ClinicalTrials.gov, PHRR) on 22 February 2024. This was followed by duplicate removal and dual independent review to finalize the inclusion list. We included trials published in or translated to English mentioning "bioprint" in their design, while we excluded those that did not adhere to our definition of bioprinting. Finally, data were charted and synthesized narratively.

Results Of 36 total search records, 11 trials met the inclusion criteria. Registration dates ranged from 2016 to 2023, with China conducting the most trials globally. Four trials had published results, while the remaining were still in progress. Four interventional trials aimed to implant bioprinted tissues made with autologous cells, including blood vessels, trachea, external ear, and wound dressings. The other seven studies were interventional and observational trials aiming to bioprint autologous cell-laden in vitro models to study conditions such as cancer.

Conclusion Bioprinting is still in the early stages of clinical research, with a focus on producing patient-specific tissues for cancer precision medicine and regenerative purposes. More standardized reporting of bioprinting-related information is needed to improve research transparency and replicability. As the body of evidence grows, our review may be used as a framework to monitor the clinical translation of bioprinting over the years.

Keywords Bioprinting, Clinical study, Clinical trial, Observational study, Scoping review, Tissue engineering, 3D printing, Bioink, Bioprinter, Implant, In vitro model

†Isabel Crisostomo and Samantha Casiguran contributed equally to this work.

*Correspondence:
Yumi Briones
Yumi.Briones@nyulangone.org
Roland Remenyi
rgremenyi@themedicalcity.com
Full list of author information is available at the end of the article

Introduction

There is a growing demand for tissue-engineered products to enter the clinical realm. Problems of organ donor shortage and transplant rejection have underlined the need for laboratory-generated implants [1]. Meanwhile, treatment failure in the clinic has emphasized the importance of using in vitro models that closely mimic human tissue for drug screening [2]. These have been the primary issues that tissue engineering has aimed to address over the years [3]. However, the traditional method of seeding cells manually into a scaffold often fails to replicate native human tissue due to low or uneven distribution of cells, presenting a hurdle for clinical translation [4, 5]. This limitation has been addressed in large part by the introduction of 3D printing to the field, birthing a technology known as bioprinting [6].

Bioprinting is the automated deposition of cells, embedded in a scaffold called a bioink, in a three-dimensional structure [7]. In contrast to manual cell seeding, bioprinting enables a uniform distribution of cells in the scaffold and a precise reconstruction of tissue architecture [5]. At the pre-clinical stage, implants have been bioprinted for connective tissue [8, 9], muscle tissue [10, 11], and skin [12]. Complex nerve structures and vasculature have also been integrated into bioprinted constructs [8, 13]. Furthermore, the automated printing process enables high-throughput production of in vitro models for disease simulation and drug screening [14]. Bioprinted models have been used to study cancer [15], liver toxicity [16], and cardiotoxicity [17].

While bioprinting has achieved clear success in the laboratory, its progress into the clinical stage is less known. Most existing reviews summarize pre-clinical bioprinting progress [18–20], with one narrative review focusing on clinical applications of bioprinting [21]. To the best of our knowledge, no review has provided a systematic framework for monitoring bioprinting efforts in clinical studies, which include interventional and observational trials that provide valuable information needed for clinical translation. Such a framework would be valuable for researchers to track the progress of bioprinting from bench to bedside. We have thus conducted a scoping review to answer the question: What is the landscape of clinical studies that have been conducted or are currently in progress involving bioprinting? Specifically, these subquestions were addressed:

1. What trends exist in the general characteristics of clinical studies involving bioprinting, particularly in terms of year posted, recruitment status, and country of origin?
2. What is the number of clinical studies implementing bioprinting for implantation compared to in vitro modeling?
3. What conditions are being addressed by bioprinting at the clinical study stage, and how are clinical studies designed to achieve this?

Through this scoping review, we aim to provide current insight on the clinical translation of bioprinting, along with a replicable framework for monitoring progress in this field over time.

Methods

This scoping review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) [22]. The review protocol was registered on Protocol Exchange (https://doi.org/10.21203/rs.3.pex-2552/v1).

Definitions

We defined bioprinting as the automated printing of live cells, embedded in a biocompatible scaffold called a bioink, in a three-dimensional structure using a device called a bioprinter [7]. Cells must be mixed with the bioink prior to printing and not deposited into an acellular 3D-printed scaffold. While the American Society for Testing and Materials (ASTM) has included such acellular constructs under their definition of bioprinting, we have opted to exclude these to focus on bioprinting as a technique that incorporates cells distinctly from manual cell seeding.

We defined a clinical study as a research study involving human participants aiming to answer a health-related question [23]. Two types of clinical studies are interventional clinical trials and observational studies. We used the revised definition of a clinical trial by the National Institutes of Health (NIH) as published in notice number NOT-OD-15-015: "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes" [24]. Meanwhile, observational studies or trials are clinical studies where health-related outcomes are assessed without assigning participants to an intervention [25]. For simplicity, we refer to both clinical and observational trials as "trials" hereafter. We further defined two categories of trials by bioprinting application: in vitro modeling (or simply "modeling") and implantation. In a modeling trial, the bioprinted construct is incorporated into the study without being integrated directly into the participant's body. Meanwhile, in an implantation trial, the bioprinted

construct is integrated directly into or onto the participant's body.

Finally, we distinguished between two types of data sources: primary registries and databases. Primary registries are digital record collections where clinical studies are directly registered. Meanwhile, databases are secondary sources that extract clinical study data from multiple registries or publications.

Data sources and search strategy

Seven data sources were selected for this review (Table 1). Five sources were databases, namely: International Clinical Trials Registry Platform (ICTRP), ScanMedicine, Cochrane Central Register of Controlled Trials (CENTRAL), National Institutes of Health Clinical Center (NIHCC), and Health Canada Clinical Trial Database (HCCTD). ICTRP and ScanMedicine cover all primary registries meeting the World Health Organization (WHO) criteria, including ClinicalTrials.gov [26–28]. CENTRAL was included to capture publications discussing trials not registered in a publicly available database [29]. NIHCC and HCCTD were included to cover trials that may not have been listed elsewhere. Meanwhile, two data sources were primary registries: ClinicalTrials.gov and the Philippine Health Research Registry (PHRR). ClinicalTrials.gov was included as it is the largest trial registry to date [30] and is likely to be frequently updated. Finally, PHRR was included as it was not covered by any other data source at the time of our search.

Our complete search strategy was published on searchRxiv (https://doi.org/10.1079/searchRxiv.2024.00466, https://doi.org/10.1079/searchRxiv.2024.00476). For data sources that accept wildcards, only the term "bioprint*" was searched. For sources not accepting wildcards, the terms "bioprint", "bioprinted", and "bioprinting" were searched. While it is possible for a trial to conform to our definition of bioprinting without explicitly using the term "bioprint", our preliminary searches found that including alternative terms such as "3D printing AND cells" returned too many irrelevant results.

Eligibility criteria and study selection

For a study to be eligible for inclusion, it must be a registered clinical study (i.e., interventional or observational trial) or a publication primarily discussing a clinical study not registered in the aforementioned data sources. The study must be published in or translated into English and must mention "bioprint" in the title, study design, or abstract. Furthermore, the study must employ bioprinting for either modeling or implantation, as defined above. We excluded studies that explicitly did not adhere to our definition of bioprinting. Only studies published before the search date, 22 February 2024, were included in the review. Otherwise, no exclusions were made based on date, location, or other study characteristics. Two authors independently assessed all studies for inclusion (i.e., dual independent review) according to these criteria using Rayyan [31]. In the case of conflicts, all authors met to reach a consensus on the inclusion decision.

Data charting and synthesis

Data from included studies were charted according to a pre-established extraction form (Supplementary Table 1). Items were selected for extraction based on three categories: general study characteristics, bioprinting-related items, and clinical study design. General study characteristics included trial identification (ID) or digital object identifier (DOI), title, URL, responsible party (i.e., sponsor or principal investigator), date first posted, date last updated, actual start date, estimated completion date, country (conducted by), country (conducted where), recruitment status, and status of results. Bioprinting-related items included the bioprinting application (i.e., model or implant), tissue type, cell type or source, and bioink. Clinical study design referred to the condition, study type, phase, description, objectives, types of

Table 1 Data sources

Data source	URL	Region covered	Data source type	Wildcard accepted?
ICTRP	https://trialsearch.who.int	International	Database	Yes
ScanMedicine	https://scanmedicine.com	International	Database	Yes
CENTRAL	https://www.cochranelibrary.com/central	International	Database	Yes
NIHCC	https://clinicalstudies.info.nih.gov	United States	Database	No
HCCTD	https://health-products.canada.ca/ctdb-bdec	Canada	Database	No
ClinicalTrials.gov	https://clinicaltrials.gov	International	Primary registry	No
PHRR	https://registry.healthresearch.ph	Philippines	Primary registry	No

ICTRP International Clinical Trials Registry Platform, *CENTRAL* Cochrane Central Register of Controlled Trials, *NIHCC* National Institutes of Health Clinical Center, *PHRR* Philippine Health Research Registry

intervention, inclusion/exclusion criteria, and primary/secondary outcome measures. Two authors manually extracted data from relevant sections of included studies while one author verified the form for accuracy.

Due to the low number of eligible studies, a narrative synthesis of the data was performed. We addressed the three sub-questions of our review, beginning with an analysis of general study characteristics, followed by a comparison of clinical studies for modeling and implantation, and ending with a summary of how each trial implemented bioprinting to address the target conditions.

Results

Study selection

Our search identified 36 records across all data sources, 17 of which were duplicates. The remaining 19 records were subjected to dual independent review. Two records found through CENTRAL were excluded for neither being nor primarily discussing clinical studies. Meanwhile, six records were excluded for not adhering to our definition of bioprinting; most commonly, these trials printed constructs with plastic rather than biocompatible material or did not print with cells. Our final inclusion list consisted of 11 clinical studies (Fig. 1). The ID and title of each included trial are listed in Table 2, while the complete extraction form is in Supplementary Table 1.

General study characteristics

Of the 11 clinical studies included in our review, seven were interventional and four were observational. Ten trials were registered publicly, while one was registered with a local hospital and discussed in a published study (Table 3). Registered trials came from two primary registries, ClinicalTrials.gov (n=7) and Chinese Clinical Trial Registry (ChiCTR) (n=3). Registration dates ranged from 2016 to 2023, with at least one new trial posted every year from 2019 (Fig. 2). The highest number of newly posted trials was in 2021 (n=4).

According to the recruitment status listed on the original trial records, the majority of trials appeared

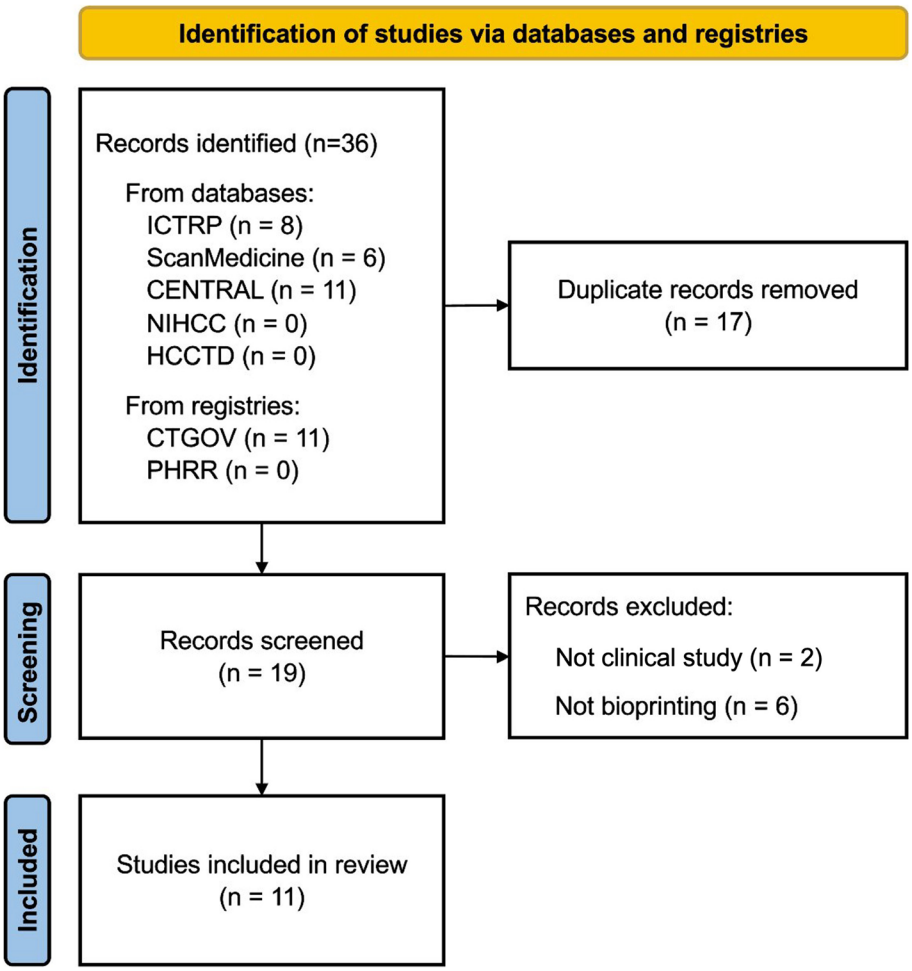

Fig. 1 PRISMA-ScR flow diagram

Table 2 Final list of eligible clinical studies

Trial ID/DOI	Public title
ChiCTR-IOR-16009658	A precision medicine-based clinical study of screening targeted drug combined with chemotherapy for the treatment of primary advanced ovarian cancer
NCT03832153	Pan-Cardio-Genetics Clot Assessment in Acute Coronary Syndromes
NCT03890614	Novel 3D Hematological Malignancy Organoid to Study Disease Biology and Chemosensitivity (Organoid)
NCT04755907	3D Bioprinted Models for Predicting Chemotherapy Response in Colorectal Cancer With/Without Liver Metastases
NCT04925323	A dermo-epidermal autologous skin substitute for further therapeutic use (BIOPSKIN)
ChiCTR2200066886	Clinical application of 3D bioprinted organoid drug screen in adjuvant chemotherapy of pancreatic cancer
NCT05955092	Exploring the Application of 3D Bioprinting for Personalized Treatment in Pancreatic Ductal Adenocarcinoma
NCT04399239	AuriNovo for Auricular Reconstruction
10.1177/15347346211045625	Management of Diabetic Foot Ulcer with MA-ECM (Minimally Manipulated Autologous Extracellular Matrix) Using 3D Bioprinting Technology - An Innovative Approach
ChiCTR2100049901	Study of the safety and efficacy of autologous stem cell 3D bioprinted blood vessels for vascular replacement in patients with peripheral limb arterial disease
NCT06051747	Patient-Customized Bioprinting Technology for Practical Regeneration of the Respiratory Tract (Trachea)

to be ongoing: either recruiting (n=5), active and not recruiting (n=1), or not yet recruiting (n=1) (Table 3). Meanwhile, one trial was terminated, one withdrawn, and one completed with published results. However, separate searching of each trial ID on Google Scholar and Dimensions AI revealed three associated publications for NCT04755907 [32], NCT05955092 [33], and NCT04925323 [34], all of which were marked as recruiting at the time of our search. Since these publications were identified outside of our search protocol, we have not included them in further analysis.

Trials were conducted by five countries worldwide, with most originating from China (n=5). Three Chinese trials were conducted by the same responsible party, Peking Union Medical College Hospital. Two trials were conducted by groups from South Korea, one of which was completed with published results but not publicly registered (Fig. 3). The United States recorded two trials, but one was terminated due to a company decision unrelated to safety. Although France and Greece also recorded conducting trials, the Greek trial was withdrawn as a result of inadequate funding.

Applications of bioprinting in clinical studies

Seven trials aimed to bioprint in vitro models, while the remaining four aimed to implant bioprinted constructs into patients (Table 4). Most trials in the modeling category were conducted by groups in China (n=5). Meanwhile, two out of four trials in the implantation category were conducted by South Korean groups (Fig. 4). Most trials in the modeling category were in the recruiting stage according to the trial record (Fig. 5). Only one trial in the implantation category was recruiting, while one was active and not recruiting. The implantation category contained the only terminated trial along with the only trial that was completed with published results.

To identify common themes across trials, we created a word cloud of the top 100 words used throughout all trial descriptions using Simplewordcloud.com (https://simplewordcloud.com/). If a description was unavailable, the trial objective or article abstract was used. Prior to word cloud generation, all duplicate words in each individual description were removed to prevent a single trial from biasing results. Words were transformed to lower case, and common English words were removed. Notable top words included "cancer", "personalized", and "regenerative" (Fig. 6).

In vitro modeling

Most trials aiming to bioprint in vitro models targeted cancer (n=5), namely, ovarian (n=1), hematological (n=1), colorectal (n=1), and pancreatic (n=2) cancers (Table 4). Three of these listed the same responsible party, Peking Union Medical College Hospital. The trials aimed to bioprint tumor tissue or organoids, and many mentioned "precision", "personalized", or "patient-specific" in the title or study design. The exact cell type and bioink were often unstated, but the cell source was discerned to be autologous tumor tissue in most cases. Only one trial (NCT03890614), targeting hematological malignancy, specified that myeloma and stromal cells were to be printed in a hyaluronic acid and gelatin-based hydrogel bioink. Three trials were observational, aiming to use the bioprinted models to predict drug sensitivity. Primary outcome measures included the response of the model to drug treatment and its correlation with patient response. The trial targeting hematological malignancy also aimed to evaluate the proportion of live to dead cells

Table 3 General study characteristics

Trial ID/DOI	Registry	Responsible Party	Registration Year	Estimated Completion Year	Country (Conducted By)	Recruitment Status	Status of Results
ChiCTR-IOR-16009658	ChiCTR	Department of Gynecology and Obstetrics, Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine	2016	2019	China	Not yet recruiting	None
NCT03832153	ClinicalTrials.gov	Aristotle University Of Thessaloniki	2019	2022	Greece	Withdrawn	None
NCT03890614	ClinicalTrials.gov	Wake Forest University Health Sciences	2019	2025	USA	Recruiting	None
NCT04755907	ClinicalTrials.gov	Peking Union Medical College Hospital	2021	2023	China	Recruiting	None[a]
NCT04925323	ClinicalTrials.gov	Assistance Publique Hopitaux De Marseille	2021	2023	France	Recruiting	None[a]
ChiCTR2200066886	ChiCTR	Peking Union Medical College Hospital, Chinese Academy of Medical Sciences	2022	2025	China	Not yet recruiting	None
NCT05955092	ClinicalTrials.gov	Peking Union Medical College Hospital	2023	2024	China	Recruiting	None[a]
NCT04399239	ClinicalTrials.gov	3DBio Therapeutics	2020	2023	USA	Terminated	None
10.1177/15347346211045625	Local hospital registry	ROKIT Healthcare, Inc.	2021[b]	2021[b]	South Korea	Completed	Published
ChiCTR2100049901	ChiCTR	West China Hospital of Sichuan University	2021	2038	China	Recruiting	None
NCT06051747	ClinicalTrials.gov	Ja Seong Bae, MD, PhD, Seoul St. Mary's Hospital	2023	2025	South Korea	Active, not recruiting	None

ChiCTR Chinese Clinical Trial Registry

[a]Results were published but not posted in the registry or database record identified by our search

[b]Year of publication

and tumor-stroma interactions in the bioprinted model. Meanwhile, two trials were interventional, with one classified as phase 2. In these cases, bioprinted models were to be used as screening platforms to optimize the delivery of treatment regimens to participants. Primary outcome measures included one-year survival rate, progression-free survival, and objective response rate. We separately found that two of these trials had published results not linked to the original trial record; namely, NCT04755907 [32] and NCT05955092 [33].

Two trials in the modeling category were not cancer-related. One observational trial registered by Aristotle University Of Thessaloniki (NCT03832153) aimed to bioprint an in vitro model to improve risk stratification for ST Elevation Myocardial Infarction (STEMI) patients. The study did not clarify the cells or bioink to be used, nor the type of tissue to be printed. Primary outcome measures were patient-centric and did not involve the bioprinted model. This trial has since been withdrawn due to lack of funding. Meanwhile, one

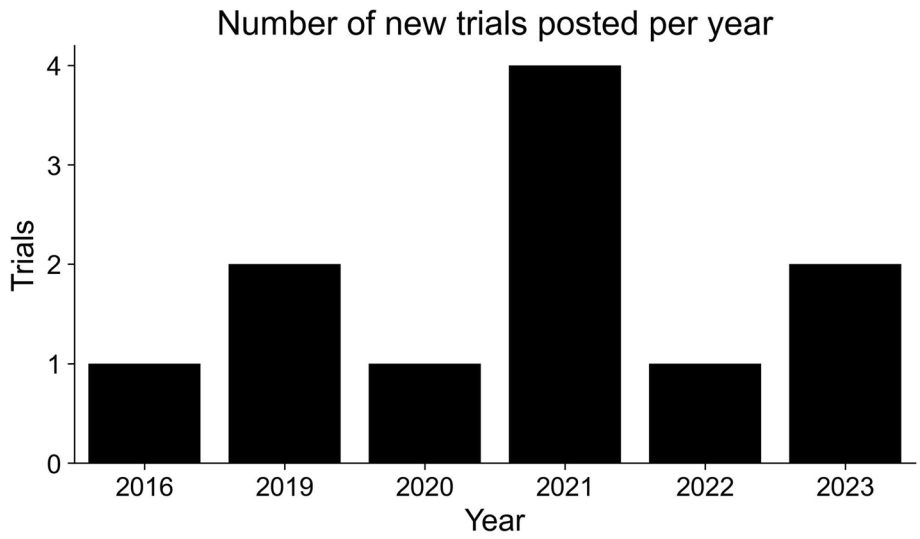

Fig. 2 Number of new trials posted per year

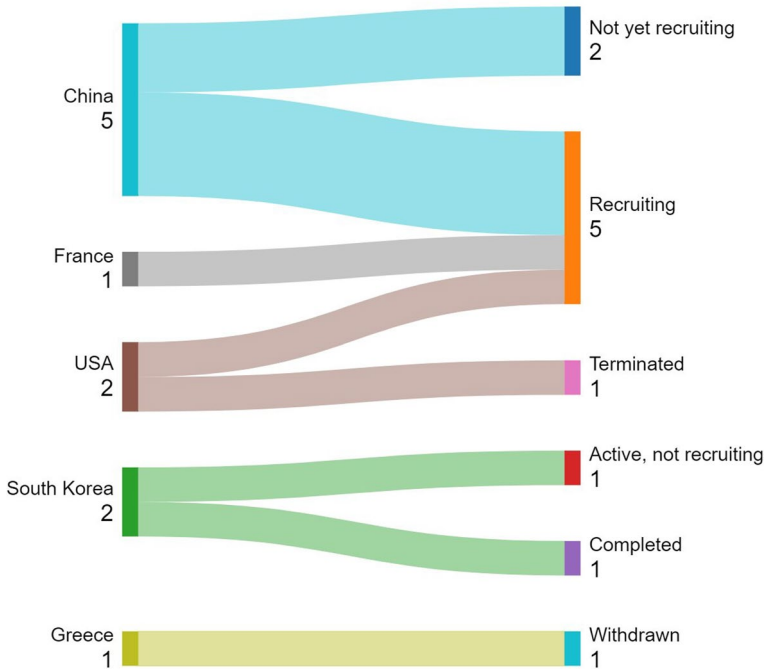

Fig. 3 Sankey diagram showing relationships between country of trial origin and recruitment status

trial at the Assistance Publique - Hôpitaux de Marseille (NCT04925323) aimed to bioprint a skin substitute with an unspecified bioink using autologous fibroblasts and keratinocytes derived from skin removed during plastic surgery. While the ultimate purpose of the skin substitute product was implantation, the trial itself was an in vitro study. Although the trial was listed as interventional, the interventions referred only to blood and skin sample collection rather than a treatment to be assessed. Primary outcome measures included sterility of the skin and population doubling rate of cells. The study was listed as "recruiting" at the time of the search; however, we separately found that results had been published in July 2023 [34].

Table 4 Clinical study design and bioprinting-related items

Trial ID/DOI	Study type	Phase	Application	Condition/s	Tissue type	Cell type/ source	Bioink
ChiCTR-IOR-16009658	Interventional	N/A	Model	Ovarian Cancer	Tumor	Autologous tumor cells	Not specified
NCT03832153	Observational	N/A	Model	STEMI, Thrombi, MicroRNA	Not specified	Not specified	Not specified
NCT03890614	Observational	N/A	Model	Hematologic Malignancy	Tumor (organoid)	Autologous myeloma and stromal cells	Hyaluronic acid and gelatin-based hydrogel
NCT04755907	Observational	N/A	Model	Colorectal Cancer, Colorectal Cancer Liver Metastasis	Tumor (organoid)	Autologous tumor tissue	Not specified
NCT04925323	Interventional	N/A	Model	Plastic Surgeries	Skin	Autologous keratinocytes, fibroblasts	Not specified
ChiCTR2200066886	Interventional	2	Model	Pancreatic Cancer	Tumor (organoid)	Autologous tumor tissue	Not specified
NCT05955092	Observational	N/A	Model	Pancreatic Ductal Adenocarcinoma	Tumor	Autologous tumor tissue	Not specified
NCT04399239	Interventional	1/2A	Implant	Microtia	Auricle	Autologous chondrocytes	Collagen hydrogel
10.1177/15347346211045625	Interventional	Unknown	Implant	Diabetic Foot Ulcer	Adipose	Autologous adipose tissue	Extracellular matrix
ChiCTR2100049901	Interventional	0	Implant	Peripheral Limb Arterial Disease	Blood vessel	Autologous stem cells	Not specified
NCT06051747	Interventional	1/2	Implant	Thyroid Cancer	Trachea	Autologous hNTSCs, hNCs	Hydrogel matrices

STEMI ST-elevation Myocardial Infarction, *hNTSCs* nasal cavity stem cells, *hNCs* nasal septum cartilage cells

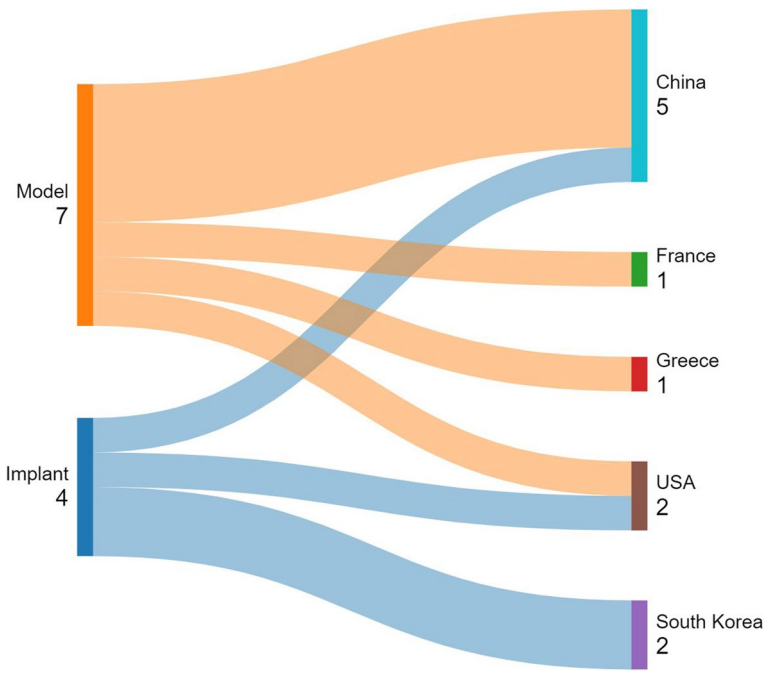

Fig. 4 Sankey diagram showing relationships between bioprinting application and country of trial origin

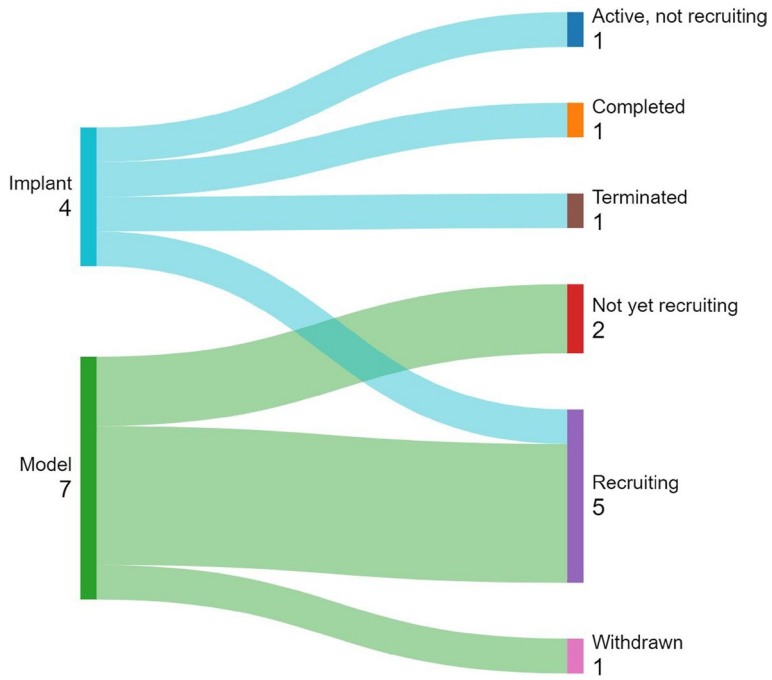

Fig. 5 Sankey diagram showing relationships between bioprinting application and recruitment status

Fig. 6 Word cloud of top 100 words from trial descriptions (made with https://simplewordcloud.com/). If a description was unavailable, the trial objective or article abstract was used. All duplicate words per description were removed. Common English words were removed

Implantation

All trials aiming to implant bioprinted tissues were interventional (Table 4). These trials often mentioned variants of the word "regenerative" in the title or description. Two trials addressed internal conditions, namely, peripheral limb arterial disease and thyroid cancer. The phase 0 trial targeting arterial disease was conducted by a Chinese hospital (ChiCTR2100049901), and it aimed to implant bioprinted blood vessels using autologous stem cells in an unspecified bioink. Primary outcome measures included device success rate, graft patency rate, and an unspecified "primary safety endpoint". This trial was still recruiting at

the time of the search. Meanwhile, the phase 1/2 trial targeting thyroid cancer was conducted by a South Korean hospital (NCT06051747), and it aimed to bioprint a personalized tracheal structure for implantation. Cells to be used were autologous nasal cavity stem cells and nasal septum cartilage cells, while the bioink was simply specified as "hydrogel matrices". Primary outcome measures included airway lumen opening rate, degree of granuloma formation, and degree of inflammation. The study was marked as "active, not recruiting".

Two trials in the implantation category targeted external conditions, namely, microtia and diabetic foot ulcers. The phase 1/2A trial targeting microtia was registered by an American company, then titled 3DBio Therapeutics and now PrintBio (NCT04399239). The trial aimed to implant AuriNovo™, an auricle bioprinted using autologous chondrocytes in a collagen bioink and customized to the patient's ear dimensions. Additional research found that the bioink (ColVivo™) and bioprinter (GMPrint™) to be used were products of PrintBio [35]. Primary outcome measures were safety (based on adverse effects) and efficacy (based on satisfaction scores). However, the trial was terminated due to a company decision unrelated to safety. Finally, one completed trial conducted by a South Korean company (ROKIT Healthcare) bioprinted wound dressings for diabetic foot ulcers [36]. Autologous adipose tissue was lipoaspirated and fragmented to produce a "Minimally Manipulated Autologous Extracellular Matrix (MA-ECM)". This was used to print custom-fitting wound patches with the Dr. INVIVO bioprinter (ROKIT Healthcare, Seoul, Korea). The patches contained adipose-derived stem cells in the native extracellular matrix, which served as the bioink. All subjects treated with MA-ECM showed complete wound healing at 12 weeks compared to only 50% of the control group. Results were published in a journal, but to our knowledge, the trial had not been posted on a public registry and only registered with the local hospital in India.

Discussion

This scoping review aimed to provide a systematic framework for monitoring the landscape of past and present clinical studies implementing bioprinting with cell-laden material. Other reviews have focused on pre-clinical bioprinting research [18–20] or have only provided a narrative summary of clinical trials involving bioprinting [21]. Through our review protocol, we identified 11 eligible interventional and observational trials, from which we extracted themes in general characteristics, bioprinting application, and trial design.

General trends in bioprinting-related trials can be compared to trends across all published studies on bioprinting as reported by Ding et al. (2023) [18]. Only 11 trials involving bioprinting were posted since 2016, which is small in comparison to over 3,000 published studies on bioprinting since 2007. This may be a reflection of the general difficulty of translating tissue engineering to the clinic [37], along with the relative newness of bioprinting as a technology. Scarcity of funding may be a challenge, with one trial having been withdrawn for this reason. However, the addition of new trials every year suggests a consistent effort to move bioprinting to the clinical stage. Most trials were conducted by groups in China, followed by the United States and South Korea. Notably, these countries were identified by Ding et al. as the global leaders in publishing and funding bioprinting research in general [18].

In vitro modeling was a more popular bioprinting application than implantation at the clinical study stage. This may be due to the added safety risks, regulations, and ethical considerations associated with implantation as an intervention [37]. Most in vitro modeling trials were observational studies targeting cancer, mirroring pre-clinical research where bioprinted cancer models have been extensively validated for drug screening and predictive purposes [38]. Importantly, two modeling trials were interventional, where information from the models was used to adapt the drug treatment administered to participants. In general, the trials in our study shared the primary aims of tissue engineering as a whole: to produce personalized disease models and regenerative implants [3].

All trials that specified cell type used autologous cells for bioprinting. The use of autologous cells is advantageous both in vitro and for implantation, as it allows for patient-specific modeling [38] and lowers the risk of implant rejection [39]. However, bioprinting with allogeneic cells at the clinical study stage remains unexplored. This presents a significant opportunity, as allogeneic cells are more efficient and economic to handle compared to autologous cells [40]. The major risk of using allogeneic cells is immune rejection; however, ways to minimize this effect are being explored [40]. Tissue engineering with allogeneic cells has been performed at the clinical study stage [41], and bioprinting with allogeneic cells has been studied preclinically [42, 43].

There were a number of limitations to consider in our study. First, our definition of bioprinting did not include acellularly printed constructs, which may be classified under bioprinting in other studies. Furthermore, several trials did not fully describe their bioprinting methods, making it unclear whether they adhered to our definition of bioprinting. Due to the limited available evidence, we decided to include all cases that did not explicitly violate our definition. We did not include grey literature sources as we wanted to prioritize registered or published trials.

Furthermore, our search strategy limited results to studies mentioning variants of "bioprint" in the database entry. We encountered one instance where our search did not capture an otherwise eligible trial listed in ICTRP (JRCT2053200022) and CENTRAL [44], as it only used the term "bio 3D printer" in the entry. Finally, we encountered instances where published results were not linked to the original trial records (which classified the trials as still recruiting). Thus, these results were not captured by our review.

We can make several recommendations based on our findings. First, there is a need for more detailed reporting of bioprinting methods in clinical studies to enhance transparency and replicability. It is also best practice for researchers to publicly register clinical studies and keep trial records updated when results are published. Proper registration would help promote transparency and reduce publication bias or selective reporting in the field [45]. To capture any published results not linked to the original trial record, an additional step can be added to our review protocol where eligible trial IDs are inputted into scientific literature search engines. Alternative data sources may also be explored, such as grey literature (e.g., bioprinting company websites and press releases), roundtable discussions with experts, or surveys conducted at bioprinting conferences. Finally, as more eligible trials are registered, future scoping reviews may choose to focus on interventional trials by checking the "Study type" section (when available as a data field in the searched database or registry) during the "Identification" phase (Fig. 1) or by filtering during dual independent review in the "Screening" phase.

Conclusion

We have presented, to our knowledge, the first scoping review of bioprinting efforts at the clinical and observational trial stage. We identified 11 trials across five countries registered from 2016 to 2023. Seven trials aimed to use bioprinting to produce in vitro, patient-derived models of disease. Meanwhile, four interventional trials aimed to implant bioprinted tissues into participants, with statuses of recruiting, active, completed, and terminated. The objectives of these trials reflected general trends in tissue engineering, namely, a focus on using autologous cells for cancer precision medicine and regenerative purposes. The limited number of eligible studies shows that bioprinting is only beginning its transition from bench to bedside. In this early stage, we posit a need for more transparency among clinical researchers in registering trials and reporting bioprinting-related information. This would enable future studies to compare bioprinting methods across trials and draw connections to clinical outcomes, when available. While progress may be slower than at the pre-clinical stage, the body of bioprinting-related trials is growing, and our review framework may be used to monitor the evolution of this field over time.

Abbreviations

ASTM	American society for testing and materials
CENTRAL	Cochrane central register of controlled trials
ChiCTR	Chinese clinical trial registry
DOI	Digital object identifier
HCCTD	Health Canada clinical trial database
ICTRP	International clinical trials registry platform
ID	Identification
MA-ECM	Minimally manipulated autologous extracellular matrix
NIH	National institutes of health
NIHCC	National institutes of health clinical center
PHRR	Philippine health research registry
PRISMA-ScR	Preferred reporting items for systematic reviews and meta-analysis extension for scoping reviews
STEMI	ST elevation myocardial infarction
WHO	World health organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41205-025-00253-2.

Supplementary Material 1: Our data extraction form is included as Supplementary Table 1 to this article.

Acknowledgements

We thank the interns of the Biomedical Research Unit who contributed to the study: Rianne Casey Yap, Pamela Manuel, Raphael Meneses, Natsumi Fukuda, and Laurenzo Roda.

Clinical trial number

Not applicable.

Authors' contributions

YB and NT performed preliminary optimization of the search protocol. All authors developed and approved the final search protocol. YB and BP executed the search. IC and SC conducted the dual independent review. YB, BP, and SC performed data charting. RR supervised the study. YB, BP, IC, SC, and NT wrote the manuscript. All authors read and approved the final manuscript.

Funding

We thank the Department of Science and Technology - Philippine Council for Health Research and Development (DOST-PCHRD) for the financial support of the authors during the development of this protocol, data analysis, and writing of the manuscript. Funding was provided as part of the 3D-HEP-DD and SkIn PaTCH projects under the Emerging and Re-emerging Diseases Program (Virology and Vaccine Research Development Program).

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files. Our data extraction form is included as Supplementary Table 1 to this article. This scoping review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR). The review protocol was registered on Protocol Exchange under the DOI number 10.21203/rs.3.pex-2552/v1. Our complete search strategy was published on searchRxiv under the DOI numbers 10.1079/searchRxiv.2024.00466 and 10.1079/searchRxiv.2024.00476.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Biomedical Research Unit, Clinical and Translational Research Institute, The Medical City, Ortigas Avenue, Pasig City 1600, Metro Manila, Philippines. [2]Vilcek Institute of Graduate Biomedical Sciences, New York University Grossman School of Medicine, 550 First Avenue, New York 10016, New York, United States of America. [3]College of Medicine, University of the East Ramon Magsaysay Memorial Medical Center Inc., 64 Aurora Boulevard, Quezon City 1113, Metro Manila, Philippines. [4]Ecology and Biodiversity, Institute for Marine and Antarctic Sciences, 20 Castray Esplanade, Battery Point 7004, Tasmania, Australia. [5]Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore.

Received: 15 August 2024 Accepted: 1 February 2025
Published online: 17 February 2025

References

1. Parihar A, Pandita V, Kumar A. 3D Printing: Advancement in Biogenerative Engineering to Combat Shortage of Organs and Bioapplicable Materials. Regen Eng Transl Med. 2022;8:173–99. https://doi.org/10.1007/s40883-021-00219-w.
2. Bose S, Clevers H, Shen X. Promises and challenges of organoid-guided precision medicine. Med. 2021;2(9):1011–26. https://doi.org/10.1016/j.medj.2021.08.005.
3. Mandrycky C, Phong K, Zheng Y. Tissue engineering toward organ-specific regeneration and disease modeling. MRS Commun. 2017;7(3):332–47.
4. Martin I, Wendt D, Heberer M. The role of bioreactors in tissue engineering. Trends Biotechnol. 2004;22(2):80–6.
5. Zhan Y, Jiang W, Liu Z, Wang Z, Guo K, Sun J. Utilizing bioprinting to engineer spatially organized tissues from the bottom-up. Stem Cell Res Ther. 2024;15(1):101.
6. Khademhosseini A, Langer R. A decade of progress in tissue engineering. Nat Protoc. 2016;11(10):1775–81.
7. Gilbert F, Viaña JNM, O'Connell CD, Dodds S. Enthusiastic portrayal of 3D bioprinting in the media: Ethical side effects. Bioethics. 2018;32(2):94–102.
8. Freeman FE, Burdis R, Kelly DJ. Printing new bones: from print-and-implant devices to bioprinted bone organ precursors. Trends Mol Med. 2021;27(7):700–11.
9. Lam T, Dehne T, Krüger JP, Hondke S, Endres M, Thomas A, et al. Photopolymerizable gelatin and hyaluronic acid for stereolithographic 3D bioprinting of tissue-engineered cartilage. J Biomed Mater Res B Appl Biomater. 2019;107(8):2649–57.
10. Kim JH, Seol YJ, Ko IK, Kang HW, Lee YK, Yoo JJ, et al. 3D bioprinted human skeletal muscle constructs for muscle function restoration. Sci Rep. 2018;8(1):12307.
11. Maiullari F, Costantini M, Milan M, Pace V, Chirivì M, Maiullari S, et al. A multi-cellular 3D bioprinting approach for vascularized heart tissue engineering based on HUVECs and iPSC-derived cardiomyocytes. Sci Rep. 2018;8(1):13532.
12. Apelgren P, Amoroso M, Säljö K, Lindahl A, Brantsing C, Orrhult LS, et al. Skin grafting on 3D bioprinted cartilage constructs in vivo. Plast Reconstr Surg Glob Open. 2018;6(9):e1930.
13. Wang T, Li W, Zhang Y, Xu X, Qiang L, Miao W, et al. Bioprinted constructs that simulate nerve-bone crosstalk to improve microenvironment for bone repair. Bioact Mater. 2023;27:377–93.
14. Mazzocchi A, Soker S, Skardal A. 3D bioprinting for high-throughput screening: Drug screening, disease modeling, and precision medicine applications. Appl Phys Rev. 2019;6(1):011302-1–12.
15. Bregenzer ME, Horst EN, Mehta P, Novak CM, Raghavan S, Snyder CS, et al. Integrated cancer tissue engineering models for precision medicine. PLoS ONE. 2019;14(5):e0216564.
16. Nguyen DG, Funk J, Robbins JB, Crogan-Grundy C, Presnell SC, Singer T, et al. Bioprinted 3D primary liver tissues allow assessment of organ-level response to clinical drug induced toxicity in vitro. PLoS ONE. 2016;11(7):e0158674.
17. Skardal A, Murphy SV, Devarasetty M, Mead I, Kang HW, Seol YJ, et al. Multi-tissue interactions in an integrated three-tissue organ-on-a-chip platform. Sci Rep. 2017;7(1):8837.
18. Ding Z, Tang N, Huang J, Cao X, Wu S. Global hotspots and emerging trends in 3D bioprinting research. Front Bioeng Biotechnol. 2023;11:1169893.
19. Mota C, Camarero-Espinosa S, Baker MB, Wieringa P, Moroni L. Bioprinting: from tissue and organ development to in vitro models. Chem Rev. 2020;120(19):10547–607.
20. Saini G, Segaran N, Mayer JL, Saini A, Albadawi H, Oklu R. Applications of 3D bioprinting in tissue engineering and regenerative medicine. J Clin Med. 2021;10(21):4966.
21. Lee SJ, Jeong W, Atala A. 3D Bioprinting for Engineered Tissue Constructs and Patient-Specific Models: Current Progress and Prospects in Clinical Applications. Adv Mater. 2024;36(49):2408032.
22. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467–73.
23. Department of Health and Human Services. Clinical Trials Registration and Results Information Submission. 2016. https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission. Accessed 27 Oct 2024.
24. National Institutes of Health. NOT-OD-15-015: Notice of Revised NIH Definition of Clinical Trial. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html. Accessed 06 Nov 2024.
25. National Library of Medicine. About ClinicalTrials.gov | ClinicalTrials.gov. https://clinicaltrials.gov/about-site/about-ctg. Accessed 27 Oct 2024.
26. World Health Organization. ICRTP Registry Network. https://www.who.int/clinical-trials-registry-platform/network. Accessed 22 Jul 2024.
27. Sadek J, Inskip A, Woltmann J, Wilkins G, Marshall C, Pokora M, et al. Scan-Medicine: An online search system for medical innovation. Contemp Clin Trials. 2023;125:107042.
28. World Health Organization. Primary registries in the WHO registry network. https://www.who.int/clinical-trials-registry-platform/network/primary-registries. Accessed 22 Jul 2024.
29. Dickersin K, Manheimer E, Wieland S, Robinson KA, Lefebvre C, McDonald S, et al. Development of the Cochrane Collaboration's CENTRAL Register of controlled clinical trials. Eval Health Prof. 2002;25(1):38–64.
30. Gresham G, Meinert JL, Gresham AG, Piantadosi S, Meinert CL. Update on the clinical trial landscape: analysis of ClinicalTrials.gov registration data, 2000–2020. Trials. 2022;23(1):858.
31. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:1–10.
32. Sun H, Sun L, Ke X, Liu L, Li C, Jin B, et al. Prediction of Clinical Precision Chemotherapy by Patient-Derived 3D Bioprinting Models of Colorectal Cancer and Its Liver Metastases. Adv Sci. 2024;11(2):2304460.
33. Sun H, Wang Y, Sun M, Ke X, Li C, Jin B, et al. Developing Patient-Derived 3D-Bioprinting models of pancreatic cancer. J Adv Res. 2024; September 14. https://www.sciencedirect.com/science/article/pii/S2090123224004132.
34. Abellan Lopez M, Hutter L, Pagin E, Vélier M, Véran J, Giraudo L, et al. In vivo efficacy proof of concept of a large-size bioprinted dermo-epidermal substitute for permanent wound coverage. Front Bioeng Biotechnol. 2023;11:1217655.
35. 3DBio Therapeutics. Aurinovo 3D-Bioprinted Ear Implant: A first-of-its-kind approach for ear reconstruction in microtia. https://mms.businesswire.com/media/20220602005051/en/1473688/1/3DBio_AuriNovo.pdf. Accessed 06 Nov 2024.
36. Kesavan R, Sheela Sasikumar C, Narayanamurthy V, Rajagopalan A, Kim J. Management of diabetic foot ulcer with MA-ECM (minimally manipulated autologous extracellular matrix) using 3D bioprinting technology-an innovative approach. Int J Lower Extrem Wounds. 2024;23(1):161–8.

37. Lu L, Arbit HM, Herrick JL, Segovis SG, Maran A, Yaszemski MJ. Tissue engineered constructs: perspectives on clinical translation. Ann Biomed Eng. 2015;43:796–804.
38. Neufeld L, Yeini E, Pozzi S, Satchi-Fainaro R. 3D bioprinted cancer models: from basic biology to drug development. Nat Rev Cancer. 2022;22(12):679–92.
39. Van der Veen VC, van der Wal MB, van Leeuwen MC, Ulrich MM, Middelkoop E. Biological background of dermal substitutes. Burns. 2010;36(3):305–21.
40. Bashor CJ, Hilton IB, Bandukwala H, Smith DM, Veiseh O. Engineering the next generation of cell-based therapeutics. Nat Rev Drug Discov. 2022;21(9):655–75.
41. Joyce K, Buljovcic Z, Rosic G, Kaszkin-Bettag M, Pandit A. Issues with tissues: Trends in tissue-engineered products in clinical trials in the European union. Tissue Eng B Rev. 2023;29(1):78–88.
42. Derr K, Zou J, Luo K, Song MJ, Sittampalam GS, Zhou C, et al. Fully three-dimensional bioprinted skin equivalent constructs with validated morphology and barrier function. Tissue Eng C Methods. 2019;25(6):334–43.
43. Varkey M, Visscher DO, Van Zuijlen PP, Atala A, Yoo JJ. Skin bioprinting: the future of burn wound reconstruction? Burns Trauma. 2019;7:s41038-019.
44. Ikeguchi R, Aoyama T, Noguchi T, Ushimaru M, Amino Y, Nakakura A, et al. Peripheral nerve regeneration following scaffold-free conduit transplant of autologous dermal fibroblasts: a non-randomised safety and feasibility trial. Commun Med. 2024;4(1):12.
45. Aslam A, Imanullah S, Asim M, El-Menyar A. Registration of clinical trials: is it really needed? N Am J Med Sci. 2013;5(12):713.

Publisher's Note