


# The Current Status of Clinical Trials on Biologics for Cartilage Repair and Osteoarthritis Treatment: An Analysis of ClinicalTrials.gov Data

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Zijun Zhang<sup>1</sup>  and Lew Schon<sup>1,2</sup>

## Abstract

**Objective.** Biologics are increasingly used for cartilage repair and osteoarthritis (OA) treatment. This study aimed to provide an overview of the clinical trials conducted on this subject. **Design.** Two-word combinations of two sets of key words “cartilage”; “joint”; “osteoarthritis” and “biologics”; “stem cells”; “cell implantation” were used to search the database of ClinicalTrials.gov and supplemented with searches of PubMed and EMBase. The registered trials were analyzed for clinical conditions, completion status, phases, and investigated biologics. Recently completed trials with posted/published results were summarized. **Results.** From 2000 to 2022, a total of 365 clinical trials were registered at ClinicalTrials.gov to use biologics for cartilage repair and OA treatment. Since 2006, the number of registered trials accelerated at an annual rate of 16.4%. Of the 265 trials designated with a phase, 72% were early Phase 1, Phase 1, and Phase 2. Chondrocytes and platelet-rich plasma (PRP) were studied in nearly equal number of early- and late-stage trials. Mesenchymal stem/stromal cells (MSCs) were the most commonly investigated biologics (38%) and mostly derived from bone marrow and adipose tissue (70%). In last 5 years, 32 of the 72 completed trials posted/published results, among which seven Phase 3 trials investigated chondrocytes, PRP, bone marrow aspirate concentrate, hyaluronic acid, collagen membrane, and albumin. **Conclusions.** There was a rapid increase in the number of registered clinical trials in recent years, using a variety of biologics for cartilage repair and OA treatment. Majority of the biologics still require late-stage trials to validate their clinical effectiveness.

## Keywords

biologics, cartilage, osteoarthritis, clinical trial, registry

## Introduction

Therapeutic biologics are components or products of living organisms for medical applications. Under this category, the U.S. Food and Drug Administration (FDA) lists “a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins” ([www.fda.gov](http://www.fda.gov)). Biologic products are increasingly used in cartilage repair and osteoarthritis (OA) treatment.<sup>1</sup> To many of the products, however, their clinical and cost effectiveness, protocol optimization and indication specification are still to be proven or validated by clinical trials.<sup>2,3</sup> The clinical applications of specific biologics or relevant therapies have been reviewed or analyzed in recent literature.<sup>4–6</sup> What is lacking is an overview of the clinical trials used a diverse array of biologics for the treatment of cartilage defect and OA, whether the trials are just initiated, ongoing, or completed,

and with or without published results. Such an overview would not only sum the accomplished clinical studies but also demonstrate trends of biologic product development and areas of clinical concerns.

ClinicalTrials.gov maintained by the National Library of Medicine at the National Institutes of Health is the largest clinical trial registry in the world. The registry publishes details of study design, intervention, outcome measures, eligibility criteria, investigator and sponsor information,

<sup>1</sup>Center for Orthopaedic Innovation, Mercy Medical Center, Baltimore, MD, USA

<sup>2</sup>Institute for Foot and Ankle Reconstruction, Mercy Medical Center, Baltimore, MD, USA

### Corresponding Author:

Zijun Zhang, Center for Orthopaedic Innovation, Mercy Medical Center, 301 Saint Paul Place, Baltimore, MD 21202, USA.  
Email: [zzhang@mdmercy.com](mailto:zzhang@mdmercy.com)



and results of the trials in a standardized format. In fact, more than half of the clinical trial results are only available at ClinicalTrials.gov.<sup>7</sup>

The goal of this study was to provide an overview of the clinical trials used biologics for the treatment of cartilage defect and OA. This study systematically examined ClinicalTrials.gov, with supplementary searches of PubMed/Medline and EMBase databases, for relevant trials. Rather than limited to one or one category of biologics, this study included a variety of biologics for cartilage repair and OA treatment. The clinical trial data were analyzed by status, phases, and categories of biologics. The results of the trials completed in the last 5 years were presented in a summary.

## Methods

1. ClinicalTrials.gov: A search of clinical trials was performed at www.ClinicalTrials.gov on January 16, 2022, using two-word combinations of two sets of key words: (1) cartilage, joint, osteoarthritis; (2) biologics, stem cells, cell implantation. No limitations and filters were applied. The returns of nine inquiries were downloaded in csv file format and assembled into one document, after removed duplicates, of 1514 trials.

Irrelevant trials were deleted, based on the following exclusion criteria: (1) trials about non-biologic implants, hemostasis, physical therapies; (2) trials about supplements/drugs via oral or intravenous administration; (3) trials collecting disease samples or about biochemical analysis; (4) biologics for imaging and diagnostic applications; and (5) trials on other medical conditions, such as rheumatoid arthritis, inflammatory arthritis, and joint infection. A total of 356 trials remained for further analysis.

2. PubMed/Medline: To implement ClinicalTrials.gov, a PubMed search was conducted on January 16, 2022, using the same nine sets of key words, with filters of "Clinical Trial" and "ClinicalTrials.gov Identifier." After removing duplicates and irrelevant papers, using the same exclusion criteria applied to the data of ClinicalTrials.gov, 16 publications were identified by nine inquiries. Of them, three had a ClinicalTrials.gov identifier unique to the ClinicalTrials.gov dataset and were manually added into the trial list of ClinicalTrials.gov.
3. EMBase: A search on EMBase was conducted on January 16, 2022, using the same nine sets of key words as for ClinicalTrials.gov and PubMed/Medline. An EMBase term "ClinicalTrials.gov" was used in each inquiry. After removed duplicates and irrelevant papers, using the same exclusion criteria applied to the data of ClinicalTrials.gov, 11 studies were identified by nine

inquiries. Of them, six had a unique ClinicalTrials.gov identifier and were manually added in the ClinicalTrials.gov trial list.

As the results of searching 3 databases, 365 clinical trials used biologics for cartilage repair and OA treatment and registered at ClinicalTrials.gov were included in this study.

4. Data sorting and analysis: In ClinicalTrials.gov, the trial phases are listed as Early Phase 1, Phase 1, Phase 2, Phase 3 and Phase 4. Based on clinical significance, this study introduced Early Phase to include Early Phase 1, Phase 1 and Phase 2, and Advanced Phase to include Phases 3 and 4. When two trial phases were indicated for a trial, the trial was counted by the lower phase.

The trial status in ClinicalTrials.gov registry is designated as active, not recruiting, by invitation, recruiting, suspended, terminated, withdrawn, completed, and unknown. For analysis, the status of the trials in this study was regrouped as incomplete (= active + not recruiting + recruiting + by invitation), terminated (= suspended + terminated + withdrawn + no longer available), complete and unknown.

The trials were sorted by the year scheduled to start, status and phase of the trials, type of biologics, disease conditions and individual joints. Particularly, the trials completed between 2016 and 2021 and having results posted in ClinicalTrials.gov database or published in journals were summarized.

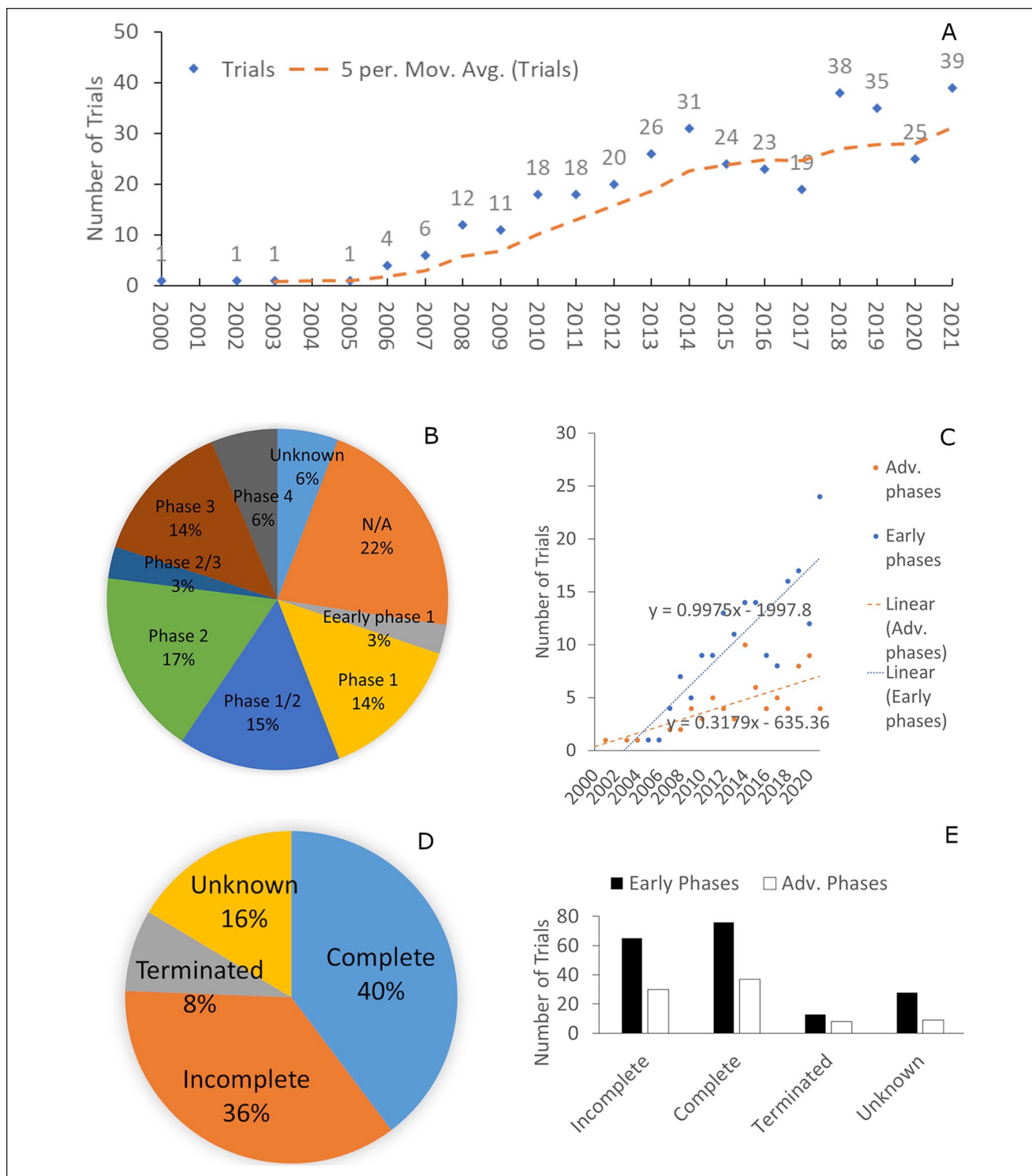
Statistical analysis: Average annual increase rate was calculated with

$$\left( \left( \frac{f}{s} \right)^{\frac{1}{y}} - 1 \right) \times 100$$

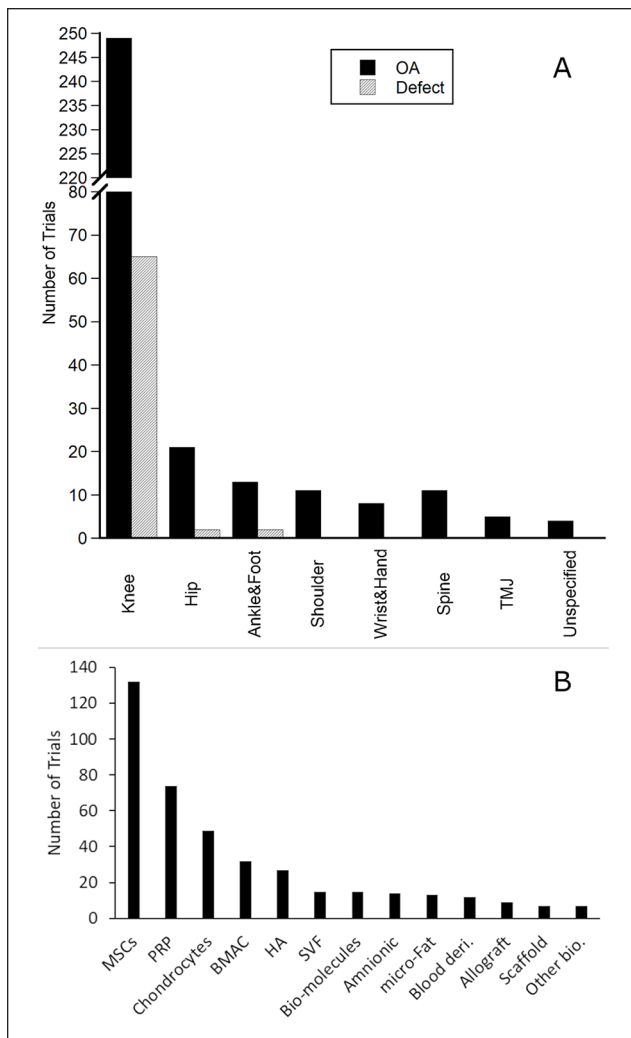
, where  $f$  is the trial number in 2021;  $s$  is the trial number in 2006;  $y$  is the number of years between 2006 and 2021. When Early Phase 1, Phase 1, and Phase 2 were combined as Early Phase, and Phases 3 and 4 were combined as Advanced Phase, the annual registration of the 2 groups was compared with Analysis of Covariance (ANOCVA).  $P < 0.05$  was set as significant. MedCalc program (version 20.009, MedCalc Software Ltd, Ostend, Belgium) was used for statistical analysis.

## Results

1. Trend of the trials: The 365 trials included in this study were started or scheduled to start between March 2000 and April 2022. Between year 2000 and 2005, there was only one or none trial registered per year. By January 16, there was 12 trials scheduled to start in the year of 2022. For a full calendar year between 2006 and 2021, the number of registered



**Figure I.** Analysis of 365 clinical trials on biologics for cartilage repair and osteoarthritis treatment. **(A)** Distribution of the 365 trials over the years. There are a few trials registered between 2000 and 2005. The annual trial registration is fluctuated but a 5-year moving trend shows steady increase after 2006. **(B)** Detailed trial phases of the 365 trials in percentages. Early Phase trials, including early Phase 1 trials to Phase 2/3 trials, make up a large collective group (52%), while Advanced trials, including Phases 3 and 4, make up 20% of the 365 trials. **(C)** The distribution of Early Phase trials vs. Advanced Phase trials over the years. The Early Phase trials increase at a more rapid pace than Advanced Phase trials. **(D)** The current status of the trials in percentage. **(E)** The trial status of Early Phase trials vs. Advanced Phase trials. Their statuses are similarly proportionated. 5. per Mov. Avg. = moving average per 5 years; Adv. Phase = Advanced Phase; incomplete = active + not recruiting + recruiting + by invitation; terminated = suspended + terminated + withdrawn.



**Figure 2. (A)** The distribution of the 365 clinical trials per joints and medical conditions. A predominant target of the trials is knee OA. Note: Several trials were designed for both osteoarthritis and cartilage defect treatments and performed on multiple joints. **(B)** Distribution of the 365 clinical trials per types of biologics used. MSCs, PRP, chondrocytes, BMAC and HA are among the most often used biologics in the trials. Bio-molecules include antibodies, antagonists, growth factors and other biologically active major molecules; Amnionic includes products from amnionic tissue/fluid, placental tissue and umbilical cord. OA = osteoarthritis; MSCs = mesenchymal stem/stromal cells; PRP = platelet-rich plasma; BMAC = bone marrow aspirate concentrate; HA = hyaluronic acid; Defect = cartilage defect; TMJ = temporomandibular joint; SVF = adipose tissue stromal vascular fraction; micro-Fat = micro-fragmented fat tissue; Blood-deri. = blood derivatives; Other bio = other biologics.

trials fluctuated but trended to increase, with an average annual increase rate of 16.4% (**Fig. 1A**).

2. Phases of the trials: There were 21 trials that did not provide information about trial phases and 79 trials entered “not applicable” for trial phase clarification.

Among the remaining 265 trials, 10 trials were classified as Early Phase 1, 51 trials as Phase 1, 56 trials as Phase 1/Phase 2, 64 trials as Phase 2, 11 trials as Phase 2/Phase 3, 50 trials as Phase 3 and 23 trials as Phase 4 (**Fig. 1B**). Of the trials designated with a phase, 72% were Early Phases and 28% Advanced Phases. The Early Phases trials increased over the years and at a greater linear coefficient than Advanced Phases (0.9975 vs. 0.32;  $P < 0.05$ , **Fig. 1C**).

3. Status of the trials: Among the 365 trials, the status of 60 trials were unknown and 145 had been completed. There were 13 trials withdrawn from the registry, 2 trials suspended, and 14 trials terminated. Among the 131 incomplete trials, 71 were recruiting, 2 were recruiting by invitation, 22 active but not recruiting, and 36 not yet recruiting (**Fig. 1D**). The Early Phase trials and Advanced Phase trials were similarly proportionated with trial status (**Fig. 1E**).
4. Trial conditions and joints: Of the 365 trials, several trials involved in multiple or unspecific joints and treated for both OA and cartilage defects. There were 322 trials (88%) for the medical condition of OA only or included OA as a sub-group (**Fig. 2A**). Majority of the trials were performed on knee OA (77%). OA in the hip, shoulder, foot and ankle, and wrist and hand were treated in much fewer number of trials. Trials also conducted on degenerative disorders of spine (the lumbar facet joint) and temporomandibular joint (TMJ).

There were 69 trials (19%) that targeted articular cartilage defects, mostly in the knee. A few trials involved in hip and ankle cartilage lesions.

5. Biologics in the trials: A wide range of biologic products were used for the treatment of cartilage defects and OA in the 365 trials (**Fig. 2B**). The leading biologics used in the trials was MSCs (36%). The second most was platelet-rich plasma (PRP; 20%). Chondrocytes, bone marrow aspirate concentrate (BMAC), stromal vascular fraction of adipose tissue (SVF), micro-fragmented fat (micro-Fat), and hyaluronic acid (HA) were the other major categories of biologics used in the trials. Disease-modification gene therapies and antibody/antagonists were developed for intraarticular delivery for OA treatment. The biologics used in the trials also included allograft (cartilage and other tissues), amniotic/placental/umbilical derived products, growth factors, blood derivatives, acellular scaffolds, hydrogel, and others.

- 5.1. MSCs: Of 132 trials, most involved in one type of MSCs but a few trials applied MSCs of different tissue origins. The common tissue origins of MSCs were bone

**Table 1.** Summary of Clinical Trials on MSCs, PRP and Chondrocytes for the Treatment of Cartilage Defect and OA.

Biologics	Number of Trials	Condition		Joint		Phase <sup>a</sup>					Status			
		OA	Defect	Knee	Other <sup>b</sup>	I	II	III	IV	Unknown	Incomplete	Complete	Terminated	Unknown
<b>Type of MSCs</b>														
BM-MSCs	48	46	2	43	6	24	12	3	1	8	10	21	5	12
AD-MSCs	49	47	2	43	6	19	9	4	1	16	22	17	1	9
UM-MSCs	36	36		35	1	20	6	3		7	16	11	2	7
B-MSCs	5	5		5		2	2			1	3	1	1	
P-MSCs	1	1		1						1				1
<b>PRP vs.</b>														
non-Treat.	31	31		22	9	3	6	7	4	11	7	17	2	5
Cell/tissue	20	20		15	5	6	6	1	3	4	9	6	1	4
HA	16	16		13	3		4	4	2	6	1	10		5
Other	10	10		8	2	2	1	1	2	6	3	3	2	2
<b>Chondrocytes</b>														
ACI	11	3	8	8	3	3	2	2	1	3	3	5	3	
Cell modi.	13	2	11	12	1	4	2	3	2	2	1	7		5
Matrix	14	2	14	13	1		1	7		6	6	6	2	
Eng. Cart.	4		4	4		1		1		2	1	1	1	1
Gene ther.	10	10		10		2	4	4			2	7		1

MSCs used in the trials were derived from bone marrow, adipose tissue, umbilical cord blood, umbilical cord, amniotic tissues, peripheral blood and dental pulp tissues. Besides 31 PRP-related trials on protocols and application regimens, 46 trials compared intraarticular injection of PRP with intraarticular injection of HA and cell/tissue biologics, such as MSCs, BMAC, SVF, micro-Fat and amniotic tissue products, and other therapies, for OA treatment. The trials of chondrocyte therapy included modification of autologous chondrocyte implantation, cellular manipulation or modification of the implanted chondrocytes, introducing matrix/scaffold and using chondrocyte-engineered cartilage. Allogeneic transduced chondrocytes were used in trials for intraarticular delivery of gene therapy for OA treatment.

MSCs = mesenchymal stem/stromal cells; PRP = platelet-rich plasma; OA = osteoarthritis; Defect = cartilage defect; BM-MSCs = bone marrow-derived MSCs; AD-MSCs = adipose tissue-derived MSCs; UM-MSCs = umbilical cord/blood derived-MSCs; B-MSCs = peripheral blood-derived MSCs; P-MSCs = dental pulp tissue-derived MSCs; non-Treat. = non-treatment control; HA = hyaluronic acid; ACI = autologous chondrocyte implantation; Cell modi. = cell modification; Eng. Cart. = engineered cartilage; Gene ther. = gene therapy; BMAC = bone marrow aspirate concentrate; SVF = stromal vascular fraction of adipose tissue.

<sup>a</sup>when two phases were indicated for a trial, the lower phase was counted.

<sup>b</sup>all joints other than knee.

marrow and adipose tissue (**Table 1**). MSCs used in the trials were also derived from umbilical cord blood or the cord, amniotic tissues, peripheral blood, and dental pulp. The majority of the MSC trials targeted at the medical condition of OA (96%) in the knee (91%). The estimated enrollment for these trials varied from 1 to 480 (median 30 and average 60 participants per trial). Among the trials, 68% were in Early Phase and 9% in Advanced Phase. About 37% of the trials were active or recruiting, 36% complete, and 6% terminated or withdrawn from the registry.

5.2. PRP: For the 74 trials about PRP, all were designed for OA treatment and enrollments were estimated from 10 to 4,000 (median 70). The trials were performed mostly on the knee (75%). Other joints in this group of trials included hip ( $n = 4$ ), shoulder ( $n = 3$ ), wrist and hand ( $n = 2$ ), ankle ( $n = 2$ ), and spine ( $n = 2$ ), TMJ and unspecified joints. Among the 74 trials, 37% were in Early Phase and 32% in Advanced Phase. Of 74 trials,

31 focused on the therapeutic effectiveness, preparation protocols, and application regimen of PRP for OA. In other trials, PRP was either compared with other biologics or as a adjunct reagent of a biologic therapy. PRP therapy was compared with HA in 16 trials for OA treatment. In 20 trials, intraarticular injection of PRP was compared with other cell/tissue biologics, such as MSCs, BMAC, SVF, micro-Fat, and amniotic tissue products, for OA treatment. Four trials compared intraarticular injection of PRP with corticosteroids and three trials compared PRP with visco-supplementation, for OA treatment. Intraarticular injection of PRP was also compared with hydrogel (NCT04519047), acetaminophen (NCT01782885), and physical exercise (NCT04697667) in OA treatment.

5.3. Chondrocytes: There were 49 cell therapy trials using chondrocytes, with estimated enrollments from 6-510 (median 46.5; average 87). Chondrocyte therapies were mostly applied for cartilage defects (71%). There

**Table 2.** Summary of Biologics Used in Clinical Trials for Treatment of Cartilage Defect and OA.

Biologics	Number of Trials	Condition		Joint		Phases <sup>a</sup>					Status			
		OA	Defect	Knee	Other <sup>b</sup>	I	II	III	IV	Unknown	Incomplete	Complete	Terninated	Unknown
BMAC	32	28	4	23	9	2	9	3	3	15	17	4	5	6
HA	27	27		24	3	4	6	5	6	6	6	16		5
SVF	15	14	1	12	3	6	3		1	5	6	5	1	3
micro-Fat	13	13		11	2	2	2	2	1	6	6	2		5
Allografts	9	5	4	6	3	1		3		5	4	4		1
A/U tissue	14	14		10	4	5	4	1	1	3	11		2	1
Bio-mol.	15	15		12	3	10	5				7	7	1	
Blood-deri.	12	12		11	1	3		7		2	1	9	1	1
Scaffold	7		7	6	2	1		1		5		3	2	4
Others	7	6	1	8		1	1		1	4	3	3		1

OA = osteoarthritis; Defect = cartilage defect; BMAC = bone marrow aspirate concentrate; HA = hyaluronic acid; SVF = adipose tissue stromal vascular fraction; micro-Fat = micro-fragmented fat tissue; A/U tissue = amniotic/umbilical tissues; Bio-mol. = bio-molecules; Blood-deri. = blood derivatives.

<sup>a</sup>when two phases were indicated for a trial, the lower phase was counted.

<sup>b</sup>all joints other than knee.

were 19 chondrocyte trials in Early Phase and 20 in Advanced Phase.

There were 11 trials used autologous chondrocyte implantation (ACI) with technical modification or in comparison with other cartilage repair procedures. They were mostly applied for repairing cartilage lesions (8/11) and in the knee (8/11). There were 13 trials featured manipulations or cellular modifications of the implanted chondrocytes. For example, there were trials supplemented autologous chondrocytes/chondrons implantation with allogeneic MSCs (NCT03672825, NCT04236739) or performed chondrogenic selection of the cultured chondrocytes before implantation (NCT00414700). Chondrocytes were implanted in the forms of cell sheet (NCT01694823), spheres (NCT01694823), or encapsulated in beads (NCT01050816). Fourteen trials incorporated extracellular matrix, synthetic scaffold, and hydrogel to ACI (NCT719576, NCT1947374, NCT560664). A series of trials ( $n = 10$ ) on intraarticular delivery of allogeneic chondrocytes with augmented transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) expression were conducted in OA joints. Four trials were conducted on implantation of chondrocyte-engineered cartilage for repairing cartilage defects.

5.4. BMAC: In 32 trials, BMAC was used mostly for OA treatment in the knee (**Table 2**). The estimated enrollment of the BMAC trials was from 6 to 4,000 (mean = 439; median = 37). In most of the trials ( $n = 27$ ), BMAC was delivered by intraarticular injection. BMAC was also applied on scaffold ( $n = 3$ ) or incorporated in osteochondral graft ( $n = 2$ ) for implantation. In eight trials, BMAC was investigated in comparison with other biologics or drugs, such as HA.

34% of the trials were in Early Phase and 19% in Advanced Phase.

5.5. HA: There were 27 trials about HA, all for OA or degenerative joints (23 in knee, 2 in hip, 1 in shoulder and 1 in TMJ). The estimated enrollment for the 27 HA-related trials was from 14 to 270 (median = 70; mean = 91). Among them, three trials investigated HA alone and 24 trials compared HA with other biologics/therapies for OA treatment (**Table 3**). 33% of the HA-related trials were in Early Phase and 41% in Advanced Phase.

5.6. SVF and micro-fat: Fifteen trials applied SVF for the treatment of cartilage defect and OA. Except of one trial (NCT05120700), in which SVF and synovial stromal cells were engineered for repairing cartilage defect, all other trials injected autologous SVF intraarticularly for the treatment of OA. For similar clinical indications, autologous micro-fragmented fat tissue was also used in the trials ( $n = 13$ ). In this SVF and micro-Fat group, 76% of the trials were Early Phase and 24% Advanced Phase.

5.7. Allograft: There were nine trials used various allogeneic tissues for OA treatment or cartilage repair. For example, meniscal allograft was used to reconstruct the osteoarthritic metatarsophalangeal (MTP) joint of the big toe and the basal joint of the thumb (NCT01673347, NCT01542515). There were several trials on neonatal cartilage (NCT00791245), osteochondral allograft or the entire joint incorporated with autologous BMAC (NCT03719417), prepared as a biologic joint, for transplantation. Decellularized osteochondral allograft was prepared and transplanted for osteochondral defect treatment (NCT02430558).

5.8. Biologic products made from amniotic tissue/fluid, placental tissue and umbilical cord/blood were investigated in 14 trials, for treatment of OA in the knee

**Table 3.** HA, in Comparison With Other Biologics, Used in Clinical Trials for OA Treatment ( $n = 24$ ).

Trial #	vs.	Condition	Major Measurements	Phase	Status
NCT03477630	PRP	Knee OA	Pain, Function	Phase 3	Active
NCT04980105	PRP, Corticosteroids	Knee OA	Timed Up and Go test (TUG), Pain	Phase 3	Active
NCT05086939	MSCs	Knee OA	Function, Pain, Radiography	Phase 3	Active
NCT04326985	MSCs	Knee OA	Function, Imaging	Early Phase I	Completed
NCT02285725	BMAC, PRP	Knee OA	IKDC score, Imaging, Requiring additional procedures	N/A	Completed
NCT01920152	PRP	Hip OA	Withdrawal for surgery, WOMAC score, Radiography	N/A	Completed
NCT02588872	PRP	Knee OA	IKDC score, Pain, Synovial fluid tests	N/A	Completed
NCT03761472	PRP	Knee OA	WOMAC score, Ultrasonography	N/A	Completed
NCT03381248	CRF	Knee OA	Adverse events, WOMAC score	N/A	Completed
NCT00225095	MSCs	Knee OA*	Imaging, Pain, Adverse events, Laboratory tests	Phase 1/2	Completed
NCT02958761	Growth factors	Knee OA	Imaging, WOMAC score, Pain, Adverse events	Phase 2	Completed
NCT04198467	PRP	Knee OA	WOMAC score, imaging	Phase 2	Completed
NCT02211521	PRP	Knee OA	IKDC score, Pain, WOMAC score, Adverse events	Phase 3	Completed
NCT02694146	PRP	Hip OA	Pain, Harris Hip Score, WOMAC score	Phase 3	Completed
NCT03825133	BMAC, PRP	Knee OA	WOMAC, KOOS, SF-36, IKDC, VAS pain scores	Phase 4	Completed
NCT03110679	BMAC	Knee OA	IKDC score, KOOS score	Phase 4	Completed
NCT02984228	PRP	Shoulder OA	SPADI score, Function, Pain, Sleep, Complications	Phase 4	Completed
NCT04711304	Wharton's Jelly	Knee OA	Adverse events, Pain, KOOS score, Imaging	Phase 1/2	Not recruiting
NCT05081921	MSCs	Knee OA	Adverse events, SF-36 form, KOOS score, Imaging	Phase 1/2	Not recruiting
NCT05027581	MSCs	Knee OA	WOMAC score, Pain, SF-36 form, Imaging	Phase 2	Recruiting
NCT03357575	MSCs	Knee OA	Adverse events, Pain, WOMAC score	N/A	Unknown status
NCT01697423	PRP	Knee OA	WOMAC score, Pain	Phase 2	Unknown status
NCT02855073	Hydrogel	Knee OA	WOMAC score, Pain, SF-36 form, Imaging	Phase 2	Unknown status
NCT02323451	Chitosan	Knee OA	Pain	Phase 4	Unknown status

HA = hyaluronic acid; OA = osteoarthritis; PRP = platelet rich plasma; MSCs = mesenchymal stem/stromal cells; BMAC = bone marrow aspirate concentrate; IKDC = International Knee Documentation Committee; WOMAC = Western Ontario and McMaster Universities Arthritis Index; CRF = cooled radiofrequency; KOOS = Knee Injury and Osteoarthritis Outcome Score; VAS = Visual Analogue Scale; SPADI = shoulder pain and disability index.

( $n = 10$ ), ankle ( $n = 2$ ), shoulder ( $n = 1$ ), and unspecified joints.

5.9. Bio-molecules: Several antibodies/antagonists against key molecules of OA pathology, such as Interleukin-1 receptor (IL-1R) and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), were developed for joint injection ( $n = 15$ ). This category included a series of trials ( $n = 5$ ) that intraarticularly delivered DNA plasmid with a variant Interleukin-10 (IL-10) transgene for the treatment of OA in the knee and lumbar spine (NCT04124042, NCT04841512). Recombinant human growth factors

(osteogenic protein-1, NCT00456157) and platelet-derived growth factor-18 (NCT01033994) were used in OA joints in two trials.

5.10. Blood-derived biologics: Blood derivatives were injected intraarticularly in 12 trials for OA treatment. A series of trials ( $n = 9$ ) were focused on a product of low molecular weight fraction of 5% human serum albumin. Autologous protein solution (APS) prepared from the cellular components of the blood was used in three trials for OA. 5.11. Scaffold: Seven trials used a variety of acellular scaffold for cartilage regeneration. The biologic scaffold

included products made of extracellular matrix (NCT05082831), bi-layer matrix made from collagen and glycosaminoglycan (NCT03808623), bi-layer scaffold featuring varied pore sizes and molecular compositions (NCT01791062).

5.12. Other biologics: There were eight trials of OA treatment used intraarticular injection of Botulinum Toxin type A (NCT01518257), hydrogel (NCT05086068), HA-based visco-supplementation products (NCT01625013) and chitosan (NCT02323451). One trial (NCT02696876) used a novel synovium harvesting device to implement microfracture procedure with implantation of autologous synovium to facilitate biological repair of cartilage.

6. Results of clinical trials in last 5 years.

Among the 365 trials included in this study, 72 trials were completed between 2016 and 2021, and 13 trials posted their results on ClinicalTrials.gov. Additionally, 19 trials published results in the journals indexed by PubMed and EMBASE (**Table 4**). Seven trials with results were phase 3 trials:

In a non-inferiority trial of ACI (NCT1222559), autologous chondrocytes were cultured in spheroids and implanted in cartilage defect in the knee ( $n = 34$ ; defect size  $2.7 \pm 0.8$  cm<sup>2</sup>).<sup>18</sup> Microfracture was performed in the controls ( $n = 32$ ; defect size  $2.4 \pm 0.8$  cm<sup>2</sup>). At 2-year follow up, the improvement of Knee Injury and Osteoarthritis Outcome Score (KOOS; **Supplementary Table 1**) was 28 points in the ACI group and 22 points in the microfracture group. The results showed that ACI is not inferior to microfracture in treating small cartilage defects.

Single and triple intraarticular injections of PRP for knee OA (mostly Kellgren-Lawrence grade 2) were compared (NCT02370420). At 12-month follow-up, both single and 3 biweekly intraarticular injections of PRP significantly reduced joint pain and improved function.<sup>19</sup> But the reduction of visual analogue scale (VAS) pain score from baseline was 86% in the triple injection group ( $n = 17$ ), whereas it was 37% in the single injection group ( $n = 18$ ;  $P = 0.02$ ). Similarly, there was greater reduction of Western Ontario and McMaster Universities Arthritis Index (WOMAC; **Supplementary Table 1**) score from the baseline data in the triple injection group (83%) than the single injection group (43%;  $P < 0.0001$ ).

Intraarticular injections of PRP and BMAC were compared for knee OA in 84 participants (NCT03289416). The PRP and BMAC were prepared with similar devices and protocols.<sup>20</sup> At 1-year follow up, both groups showed similar improvements in WOMAC and International Knee Documentation Committee (IKDC; **Supplementary Table 1**) scores over their baselines.

Intraarticular delivery of BMAC via superolateral, anteromedial, and anterolateral portals of knee arthroscopy

were compared in 111 knee OA patients (NCT03825133).<sup>21</sup> The improvements of KOOS, WOMAC, and VAS pain scores were not statistically different among the three portals of BAMC delivery at days 3, 7, 14, and 21 post-operatively.

To treat cartilage defect, a collagen membrane was either glued or sutured to cover the defect after microfracture (NCT02993510). The group of microfracture with a membrane coverage over the defect ( $n = 30$ ) sustained improvement ( $>80$ ) of Modified Cincinnati Score (**Supplementary Table 1**) from the baseline data at 5-year follow-up, while the microfracture alone group ( $n = 9$ ) initially improved over the baseline in the first 2 years but lost the gains in 5 years ( $<60$ ;  $P < 0.05$ ).<sup>22</sup>

HA was injected into the TMJ after arthroscopy for TMJ disorder in 26 patients and 25 patients had arthroscopy alone (NCT04110587). No differences were observed between the two groups in VAS pain score, maximum mouth opening, and disk position by MRI at months 3, 6, 9, and 12.<sup>23</sup>

The ultra-filtrate ( $<5$  kDa) of 5% human serum albumin was injected into OA knees ( $n = 144$ ; Kellgren-Lawrence grade 4; NCT3182686). The control group injected saline. Assessed with OMERACT-OARSI responder criteria,<sup>24</sup> 71% (95% confidence interval: 63%–78%) of the albumin group were responders at 3 months, which exceeded the 30% threshold for clinical benefit.<sup>25</sup>

## Discussion

This study analyzed 365 trials that used biologics for the treatment of cartilage defect and OA, and registered at ClinicalTrials.gov. In contrast to only four trials registered between 2000 and 2005, trial registration accelerated after 2006. The increased clinical trials on this subject may attribute to a growing clinical interest, increased availability of commercial biologics, and regulatory and public demand.<sup>26</sup>

Of the 365 trials, more than 70% were Early Phase trials (from early phase 1 to phase 2), which investigates the safety and effectiveness of a biologic product in small groups of patients. The Early Phase trials registered at a faster pace than the Advanced Phase (phases 3 and 4) trials during the same period. Although they are essential for moving any biologics toward clinic applications, Early Phase trials have much less immediate clinical impacts.

Majority of the 365 trials targeted OA in the knee, which is in line with a high prevalence of knee OA.<sup>27</sup> Among a group of diverse biologics used in the trials, MSCs accounted for more than a third of the trials (132/365). It is evident of aggressive clinical translation of recent progresses in stem cell and cartilage research.<sup>28</sup> There were, however, far fewer Advance Phase trials than Early Phase trials (12 vs. 94). Recently completed Early Phase trials showed no serious adverse events after intraarticular injections of umbilical



**Table 4.** Clinical Trials on Biologics for the Treatment of OA and Cartilage Defect Completed Between 2016 and 2021 and Having Posted/Published Results (*n* = 32).

NCT Number	Condition	Biologics	Phase	Subjects	Brief Outcomes
NCT01931007	Knee OA	BMAC	1	25	No serious adverse events in 6 mo. <sup>54</sup>
NCT02993510	Knee Cart. Def.	Chondro-Gide	3	47	Improved microfracture procedure at 5 yrs. <sup>22</sup>
NCT02162693	Knee OA	MSCs vs. HA	2	25	Greater reduction of pain scores by MSCs. <sup>8</sup>
NCT02658344	Knee OA	MSCs	2	24	Reduced pain scores, increased range of motion at 6 mo. <sup>30</sup>
NCT03527693	Knee OA	micro-Fat	N/A	38	No treatment-related adverse events. <sup>9</sup>
NCT02580695	Knee OA	MSCs, HA	1/2	26	MSCs (two doses) reduced pain scores at 1 yr. <sup>29</sup>
NCT02697682	Knee OA	micro-Fat	N/A	20	Improved KOOS scores in 1 yr. <sup>10</sup>
NCT03825133	Knee OA	BMAC	4	111	Improved WOMAC, KOOS, IKDC scores in 1 yr. <sup>11</sup>
NCT03182686	Knee OA	Ampion	3	168	Significant more responders at 3 mo. <sup>25</sup>
NCT01225575	Knee Cart. Def.	chondrosphere	2	73	Improved KOOS, IKDC scores at 5 yrs. <sup>46</sup>
NCT02641860	Knee OA	MSCs	1	18	Improved WOMAC scores at 1 yr. <sup>12</sup>
NCT01605201	Knee Cart. Def.	Engineered Cart.	1	10	No adverse events, Improved KOOS and IKDC scores at 2 yrs. <sup>47</sup>
NCT02351011	Knee OA	MSCs	1/2	12	No serious adverse events, improved pain and stiffness at 1 yr. <sup>31</sup>
NCT04110587	TMJ Disorders	HA	4	51	No improvement in pain score and maximal oral opening. <sup>23</sup>
NCT03130335	Knee OA	BMAC	N/A	13	Improved KOOS Jr. score, no serious adverse events. <sup>55</sup>
NCT04454164	Knee OA	PRP	1	237	Improved VAS-pain, KOOS, WOMAC scores at 1 yr. <sup>49</sup>
NCT01222559	Knee Cart. Def.	chondrosphere	3	102	No inferiority to microfracture. <sup>18</sup>
NCT03289416	Knee OA	PRP vs. BMAC	4	84	No difference in WOMAC and IKDC scores. <sup>20</sup>
NCT04352075	Knee OA	micro-fat, PRP	1/2	27	Micro-fat alone reduced WOMAC and VAS pain scores at 6 mo. <sup>13</sup>
NCT02230956	Knee OA	Botulinum toxin	2	158	No difference with placebo in pain score in 6 mo. <sup>14</sup>
NCT02037204	Knee Cart. Def.	Chondrons, MSCs	1/2	35	No serious adverse events, improved KOOS score at 18 mo.
NCT02370420	Knee OA	PRP (1 vs. 3 doses)	3	35	Reduced pain scores at 1 yr. by 3 doses. <sup>19</sup>
NCT02262364	Knee OA	APS	1	10	1 serious adverse event, improved pain scores at 1 yr.
NCT01733186	Knee Cart. Def.	MSCs	1/2	12	No serious adverse events, improved IKDC, pain, KOOS scores.
NCT02958267	Knee OA	BMAC+PRP vs. HA	2	32	No difference between BMAC+PRP and HA groups. <sup>56</sup>
NCT02674399	Knee OA	MSCs	2	26	Improved WOMAC, VAS pain scores at 1 yr.
NCT03257371	Knee OA	Biologic Joint	N/A	9	Reduced VAS pain score, 2 serious adverse events
NCT01625013	Knee OA	Synvisc-One	N/A	48	86% Minimal Clinical Important Improvement at 6 mo.
NCT02726945	Knee OA	SVF	N/A	39	No serious adverse events, reduced WOMAC score at 1 yr. <sup>57</sup>
NCT01920152	Hip OA	PRP, HA	N/A	33	PRP reduced WOMAC score and delayed hip replacement. <sup>15</sup>
NCT03381248	Knee OA	HA vs. CRFA	N/A	177	CRFA reduced more pain and WOMAC scores at 6 mo. <sup>16</sup>
NCT02138890	Knee OA	APS	N/A	46	Improved WOMAC, KOOS and VAS pain scores at 3 yrs. <sup>17</sup>

OA = osteoarthritis; BMAC = bone marrow aspirate concentrate; Cart. = cartilage; MSCs = mesenchymal stem/stromal cells; HA = hyaluronic acid; micro-Fat = micro-fragmented fat tissue; KOOS = Knee Injury and Osteoarthritis Outcome Score; WOMAC = Western Ontario and McMaster Universities Arthritis Index; IKDC = International Knee Documentation Committee; TMJ = temporomandibular joint; PRP = platelet rich plasma; VAS = Visual Analogue Scale; APS = autologous protein solution; SVF = adipose tissue stromal vascular fraction; CRFA = cooled radiofrequency ablation.

cord-derived MSCs,<sup>29</sup> adipose tissue-derived MSCs<sup>30</sup> or bone marrow-derived MSCs.<sup>31</sup> Still, regulations and standardized protocols of processing, storage, transplantation and administration are required to guard the safe application of MSCs.<sup>32</sup> In small cohorts, the injected MSCs showed to improve pain and functions of the OA joints. In a phase 3 trial (NCT01041001, NCT01626677), implantation of umbilical cord-derived MSCs in knee cartilage defects exceeded the minimal clinically important difference (MCID) for pain and function improvements at 5-year follow up.<sup>33</sup> A meta-analysis of 13 randomized controlled clinical trials, including a total of 434 participants, however, concluded that intraarticular injection of MSCs has no therapeutic effect on OA.<sup>34</sup> Randomized controlled phase 3 trials, with sufficient sample sizes, are needed to validate the effectiveness of MSC therapies for cartilage repair and OA treatment.

Unlike MSCs, chondrocytes were used more in Advanced Phase trials than Early Phase trials. Developed from the original ACI technique,<sup>35</sup> recent trials addressed the biological properties of the chondrocytes, such as the chondrogenic potential of the implanted chondrocytes (NCT719576, NCT414700).<sup>36,37</sup> Autologous chondrocytes were isolated as chondrons (NCT04236739, NCT02037204), which retain the pericellular matrix of the isolated chondrocytes and are more robust in matrix production and viability than chondrocytes.<sup>38,39</sup> The concept of chondron was also introduced to mix autologous chondrocytes with fibrin before implantation (NCT1050816). Autologous chondrons and allogeneic MSCs were combined for implantation for enhanced chondrogenesis (NCT02037204).<sup>40</sup> The matrix/scaffold used in ACI trials not only facilitates the handling of chondrocytes during surgery but also provides the implanted chondrocytes 3-dimensional anchorage,<sup>37,41-44</sup> which is essential to stabilize chondrocyte phenotype, maintain high viability and increase matrix production.<sup>45</sup> In the same line of strategy, there were trials to grow autologous chondrocytes in the forms of cell sheet or spheres for implantation (NCT01225575, NCT01222559, NCT01694823).<sup>18,46</sup> A recent trial used nasal cartilage as a source of autologous chondrocytes and cartilage engineering (NCT01605201).<sup>47</sup> Allogeneic transduced chondrocytes were used for intraarticular delivery of gene therapies for OA (NCT2072070).<sup>48</sup>

PRP was another biologic product more commonly used in the trials for OA treatment. Trials (NCT02370420, NCT04454164) demonstrated that multiple intraarticular injections increased the efficacy of PRP and extended the duration of its therapeutic effects for knee OA.<sup>19,49</sup> A big topic of the PRP trials was to gauge its efficacy, in comparison with other biologics, such as BMAC (NCT03289416)<sup>20</sup> and HA (NCT01670578, NCT02211521), for OA.<sup>50,51</sup> Varied PRP preparation protocols used in the trials were a

source of controversy of how PRP should be defined or standardized.<sup>52</sup>

Although it is controversial to characterize BMAC and SVF as minimally manipulated MSCs,<sup>53</sup> they were used as such in a number of trials (NCT01931007, NCT03825133, NCT03130335, NCT03289416, NCT02958267, NCT02726945) for OA treatment. The available results of these trials indicated both BMAC and SVF were safe and therapeutic for OA applications.<sup>20,21,54-57</sup>

Tissue biologics used in the trials for cartilage repair and OA treatment included micro-fragmented fat, particulated neonatal cartilage, and micronized particulate amnion and umbilical cord. Blood derivatives, antibodies, antagonists, growth factors and gene therapies used in the clinical trials targeted more specific OA pathologies. This class of biologics presented great diversity of biologic products and were used mostly in the Early Phase trials, with a few posted or published outcomes.

Because of considerable variables a biologic product inherited by its biological origin and built in during processing, several clinical trials may be needed to reach a consensus on its clinical effectiveness.<sup>58</sup> ClinicalTrials.gov provides a portal to access relevant clinical trials and monitor their progress. Detailed trial protocols published by the registry are not often available in research articles. In this study, 7 of the 32 recently completed trials posted their results only at ClinicalTrials.gov. Additionally, the trials ended by suspension, termination and withdrawn may have valuable information but are rarely published in journals.

In summary, the 365 clinical trials registered at ClinicalTrials.gov demonstrated a rapid increase of using biologics for the treatment of cartilage defect and OA. A large portion of the trials used MSCs for the treatment of OA but they were mostly Early Phase trials. This study showed that ClinicalTrials.gov is a useful source of information about biologics for cartilage repair and other applications.

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Not applicable.

### ORCID iD

Zijun Zhang  <https://orcid.org/0000-0003-1281-9964>

## Supplemental Material

Supplementary material for this article is available on the *Cartilage* website at <http://cart.sagepub.com/supplemental>.

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