Research Article

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Regenerative Medicine

Publication rates and reported results in a cohort of gene- and cell-based therapy trials

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Aim: We investigated publication rates and reported results for gene- and cell-based therapy trials. **Materials & methods:** In a cohort of Institutional Review Board (IRB)-authorized trials during 2007–2017 in the Netherlands (n = 105), we examine publication rates and reported results in scientific papers and conference abstracts as well as associations with the occurrence of trial characteristics. **Results:** The publication rate for scientific papers was 27% and 17% for conference abstracts (median survival time: 1050 days). Academic hospitals published more in scientific papers whereas private sponsors published more in conference abstracts. Manufacturing protocols were underreported compared with clinical outcomes. Most publications reported positive results (78%). **Conclusion:** Publication rates are currently suboptimal indicating a need for enhanced knowledge sharing to stimulate gene- and cell-based therapy development.

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Keywords: academic research • clinical trial cohort • clinical trial transparency • commercial development • conference abstract • drug regulatory science • gene- and cell-based therapies • publication bias • scientific publication

It is well established that developers of gene- and cell-based therapies (GCTs) face numerous scientific, technological and manufacturing challenges when translating new discoveries from bench to bedside [1,2] and when scaling up for industrial manufacturing [3]. Scientific uncertainties and technological hurdles [1,2,4,5] currently complicate standardization of regulatory requirements and guidance for clinical development of GCTs. Timely publication of GCT clinical trial results, through publication of scientific papers or conferences abstracts, can mitigate this problem [3]. Yet, underreporting of trial results had caused much debate over the last few years, in particular for privately sponsored drug trials [6]. For emerging fields such as the GCT field, no information is available on the publication of trial results.

Previous work on publication of drug trial results shows that drug trial results are underreported in scientific literature. A meta-analysis reported publication rates ranging between 22–72% of trials, with a weighted pooled rate of approximately 45% [7]. Individual studies reported higher publication rates between 50–70% [8–10], although these relatively high publication rates appear to be linked to late phase development. Two of these studies include late phase trials [9,10], while another shows that Phase I trials are associated with nonpublication [8]. Phase I drug trials typically include healthy subjects to assess safety and pharmacokinetics, which may be less interesting to publish compared with patient data and result in nonpublication of first-in-man trials [8]. Furthermore, underreporting of drug trial results is attributed to nonsignificant or negative clinical outcomes, which creates a publication bias toward positive clinical outcomes [11–14]. Therefore, it is postulated that enhanced publication of drug trial results, including negative clinical outcomes, is vital to prevent duplication of research efforts and biases in medical information that impact clinical practice [15–17].

The need to improve scientific publication rates and dissemination of trial result via other channels is even more pressing in the GCT field due to scientific and technological uncertainties and other hurdles that hamper

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development [18]. Importantly, GCT trials differ from other drug trials, which may lead to different patterns of publication. First, most GCTs in the European Union (EU) are still in early stage development [19–21], which may limit publication potential similar to limited publication of early stage drug trials [8]. However, similar to the field of oncology [22], GCTs are likely to be administered directly to patients instead of healthy volunteers in early phase development, with greater potential for publication. Second, the field of GCTs consists of heterogenous technologies that are designed to target a diverse range of therapeutic areas [23,24]. Designs of GCT technologies are highly specific, with challenges of their own [1]. The state of clinical development may vary between therapeutic areas and technologies due to varying levels of scientific and technological advance and influence publication. Third, studies consistently show that large proportions of GCT trials are sponsored by academic hospitals and small- and medium-sized enterprises instead of large industries [19–21]. Academic GCT trial sponsors report to aim for generation of knowledge and optimizing experimental technologies [25] instead of commercialization. Academics have incentives to publish results in scientific papers and to engage in scientific meetings (e.g., conferences, symposia), workshops and consortia [25,26]. Furthermore, academic hospitals are likely to have scientific, technological and clinical experience under one roof and have capabilities to generate different types of knowledge [27], such as manufacturing and quality outcomes and proof of mechanism (biological activity). Therefore, publication rates may be higher for publicly sponsored GCT trials compared with private sponsored GCT trials. However, other studies show that conference attendance and scientific publication by private sponsors are linked to commercial incentives [28,29] and may drive publication rates up for private sponsors.

Against this background, the study aims to provide insight into publication rates for both scientific papers and conference abstracts and associations with trial characteristics (i.e., sponsor, product characteristics and trial design) in a GCT trial cohort. Furthermore, we investigate the type of results reported, distinguishing between clinical outcomes and manufacturing and quality outcomes.

Materials & methods

Data collection

Clinical trial cohort

In order to create a cohort of GCT trials, we selected all GCT trials that were authorized in the Netherlands from 2007 until the end of 2017. GCT trial applications are centrally reviewed and authorized by the Dutch central Institutional Review Board ('Centrale Commissie Mensgebonden Onderzoek', referred to as IRB from hereon). Data on GCT trials was extracted from the publicly available IRB trial registry (www.toetsingonline.nl) in May 2018. Methods were adapted from previous work [8,30].

GCT trials were selected from the IRB database by using the European definition of advanced therapy medicinal products and the Dutch definition of somatic cellular therapy [31]. The latter definition is wider than the definition of somatic cell therapy medicinal product. Search terms for the IRB database included 'somatische celtherapie' (somatic cell therapy), 'xenogene celtherapie onderzoek' (xenogenic cell research), 'gentherapie' (gene therapy), 'genetisch gemodificeerde organismen' (genetically modified organisms), 'weefselmanipulatie' (tissue manipulation), 'tissue manipulation' and 'tissue engineering'. Trial hits were manually selected using the following exclusion criteria: chemical based drugs, noncellular-based biological medicines, surgical procedures, medical devices and vaccines for immunization against infectious disease as well as noninterventional trials that involved gene or cellular source material such as *in vitro* studies with human blood samples. In case of secondary trial authorizations (e.g., protocol amendments), the first authorization date was used for analysis.

Search for publications & conference abstracts

For all included GCT trials, we performed a search for publications of trial results during the period from authorization until July 2018, allowing for a minimal follow-up of 6 months for each trial. Building on an adapted search algorithm from a previous study [30], we used Google Scholar, PubMed and EMBASE in a consecutive order to search for scientific papers and conference abstracts or posters. We started the search in Google Scholar using the identifiers of the IRB, EudraCT and clinicaltrials.gov registries, if available, because most journals mandate to publish this identifier. To mitigate the risk of missing publications without trial identifier, we additionally use search terms in PubMed and EMBASE that included a combination of name of GCT product, indication, sponsor name and registry identifier. EMBASE was included in the search algorithm to search for conference abstracts and posters and to supplement findings from Google Scholar and PubMed. EMBASE lists numerous conference abstracts since 2009 (>180,000) and key GCT target journals that publish conference abstract proceedings (*Cytotherapy,*

Molecular Therapy, *Journal of Clinical Oncology*, *Annuals of Oncology*, *Blood*). Registry identifiers were used to match trials and publications. If the registry identifier was not available, information on sponsor, study center, trial name, chronology of trial and publication, investigators, indication, name of GCT product and comparator(s) were used to establish a match. If matching remained inconclusive due to discrepancies on one or more of these criteria, the publication was disregarded.

Outcome measures

The main outcome measure of publication was defined as a binary outcome variable of scientific publication. Scientific publication is defined as publishing findings in scientific, peer-reviewed papers during the period from authorization until 1 July 2018. In addition, a sensitivity analysis was performed to assess the scientific publication rate with at least median follow-up (authorized until 1 January 2014; 4.5 years). The secondary outcome measure was defined as a binary outcome variable of conference abstract publication. Conference abstract publication is defined as publishing findings in conference abstracts or publicly available posters during the period from authorization until 1 July 2018. Publication in the EudraCT trial registry was also considered as a planned outcome measure. However, this outcome measure was omitted from the analysis due to the low number of trials with this outcome (n = 2).

Per publication, the type of reported knowledge was categorized into clinical outcomes and/or manufacturing and quality outcomes. Clinical outcomes include all outcomes that relate to responses of trial subjects to GCT treatment, whereas manufacturing and quality outcomes include all manufacturing protocols and quality control methods that only relate to the product. Clinical outcomes were categorized (not mutually exclusive) into reporting of clinical tolerability/safety, proof of interaction and/or affecting target biological systems such as immune system and/or clinical evidence related to effects on disease biomarkers or surrogate end points and clinical evidence related to effects on clinical end points/clinical activity.

Per scientific paper, it was assessed whether scientific papers reported detailed manufacturing and quality outcomes defined as extensive reporting of manufacturing protocols and quality control methods (1) or not (0). Per conference abstract, it was assessed whether it contained statements on manufacturing steps or quality specifications (1) or not (0). References to previous publications or supplementary material were included for categorization.

Furthermore, based on the conclusions of the authors in abstract or the discussion/conclusion section in scientific papers, it was assessed per publication whether trial results were considered negative (0), positive (1) or that the publication did not report outcomes (2). For publications that reported clinical outcomes, negative results (0) were defined as evidence that was considered supportive of discontinuation of further clinical development with the product, either demonstrated based on substantial toxicity, safety but no indications of beneficial responses on clinical outcomes. For publications that reported clinical outcomes, positive results (1) were defined as evidence that was considered supportive of continued clinical development with the product, either demonstrated based on effects on biological systems such as immune responses, safety and feasibility or positive outcomes on end points. For publications that reported in-detail manufacturing and quality outcomes only, it was assessed whether the manufacturing protocol and quality methods were considered useful (1 – positive) for continued product development or not (0 – negative). Positive manufacturing outcomes were defined as evidence that demonstrated feasibility, robustness or success to manufacture under GMP conditions, under conditions of distribution or to manufacture comparable batches among manufacturing sites. Publications that exclusively reported clinical trial designs, without any clinical or manufacturing and quality outcomes, were defined as no results (2).

GCT trial characteristics

Building on previous work [30], we selected trial characteristic that could be associated with publication, First we selected characteristics to capture specifics of the GCT developer landscape and product characteristics. All trials had one sponsor, which were divided into public and private sponsors. Public sponsors were categorized into academic hospitals and other public sponsors (e.g., blood or tissue banks). Private sponsors included small private entities (small US businesses and EU small and medium-sized enterprises) and large industry. Second, other trial characteristics included known determinants for publication of drug trials, such as trial phase [8], and trial characteristics that are specific to GCTs, such as the active substance. Information on trial characteristics was primarily extracted from the IRB registry and coded into predefined categories (Supplementary Table 1). We supplemented missing data in the IRB registry with information from EudraCT (www.clinicaltrialsregister.eu). Other variables that relate to trial progression (e.g., start of patient enrollment, trial completion) and planned

number of participants were omitted due to incomplete or unreliable information in the public registries. Candidate variables that relate to study objectives and defined end points were not selected due to the heterogeneity of the GCT field and the variance for appropriate study design among products.

Data analysis

To illustrate publication proportions over time, trials were stratified and tabulated by year of IRB authorization and by publication in scientific papers and conferences abstracts. We performed a Pearson correlation test to inspect strong correlations between trial characteristics, using $r > 0.5$ as rule. To illustrate how trial sponsors published different types of knowledge, publications were stratified and tabulated by publication type and further stratified by sponsor and reported knowledge.

The end of follow-up was defined as 1 July 2018 for trials without publication outcome or the date of the first scientific paper for trials with the outcome of scientific publication and the date of the first conference abstract for trials with the outcome of publication through conference abstracts. To account for variation in duration of follow-up, we performed univariate Cox regression analysis to calculate associations between trial characteristics and the outcome measures of time to publication in scientific papers (analysis 1) and conference abstracts (analysis 2). We calculated crude hazard ratios, 99% CIs and p-values. We did not perform multivariable Cox regression, because of limitations of the dataset (small number of events, correlations and multicollinearity between trial characteristics). The significance threshold was set at 0.01 to account for multiple analyses. For the Cox analysis, we excluded publications that were published before the date of trial authorization in the Netherlands (e.g., multicenter trials initiated earlier and with published outcomes in other countries). In addition, we performed a *post hoc* sensitivity analysis of the publication rate for trials with a follow-up of more than 4.5 years (authorized until 1 January 2014). We used IBM SPSS Statistics version 24 for all data analyses.

Results

Between 2007 and the end of 2017, 139 applications for trial authorization were submitted to the IRB. Of these applications, 34 applications (24%) were rejected (Figure 1). Thus, our clinical trial cohort consists of 105 authorized GCT trials in the Netherlands. The scientific publication rate was 27%, versus a 17% conference abstract publication rate after excluding two outcomes of scientific publications and nine outcomes of conference abstract publication because they were published before IRB authorization (median survival time 1050 days). The scientific publication rate of trials with at least median follow-up of 4.5 years was 49% (n = 23/47).

Cohort characteristics

Trials

Two-thirds of all trials were sponsored by public sponsors (67%) and a third of all trials were sponsored by private entities (33%). Public sponsors were mainly academic hospitals (n = 56 trials; 54% of all sponsors) versus other public sponsors (n = 14 trials; 13% of all sponsors; Table 1). Private sponsors consisted of small companies (n = 19 trials; 18% of all sponsors) and large industry (n = 16 trials; 15% of all sponsors). Most trials were conducted with cell therapies (76%) compared with gene therapies (24%). The GCT trials included either stem cells or other somatic cells (47%), lymphocytes (19%), dendritic cells (20%) or gene-delivery vectors (14%) as the active substance. Trials were equally distributed between oncology and other disease areas, early and late phase development and randomized and other designs (Table 1). The median survival time for the trials interquartile range (IQR) was 1050 days (426–1674 days).

Sponsor, center and geographic location of trials were strongly correlated. Academically sponsored trials are almost exclusively, single-centered, Dutch trials, whereas most privately sponsored trials and trials sponsored by other public sponsors are multicentered, multinational trials. Furthermore, randomized design and study phase and product type and active substance are strongly correlated. Early phase trials mostly have nonrandomized designs, whereas late phase trials mostly have randomized design. Stem cell and dendritic cell-based therapies are exclusively cell therapies, whereas vectors are exclusively gene therapy. Lymphocyte based therapies are classified as both gene (n = 10) and cell therapies (n = 11). The median survival time (IQR) for single-center trials (1428 days [799–2057 days]) is approximately twice as high compared with multicenter trials (744 days [113–1375 days]).

Figure 2 shows the number of authorized trials per year, stratified by publication outcome. Clinical trial authorizations increased from one trial in 2007 to 20 trials in 2017. Approximately half of all clinical trial authorizations occurred before 2014 and the other half from 2014 onwards. Results were more often scientifically

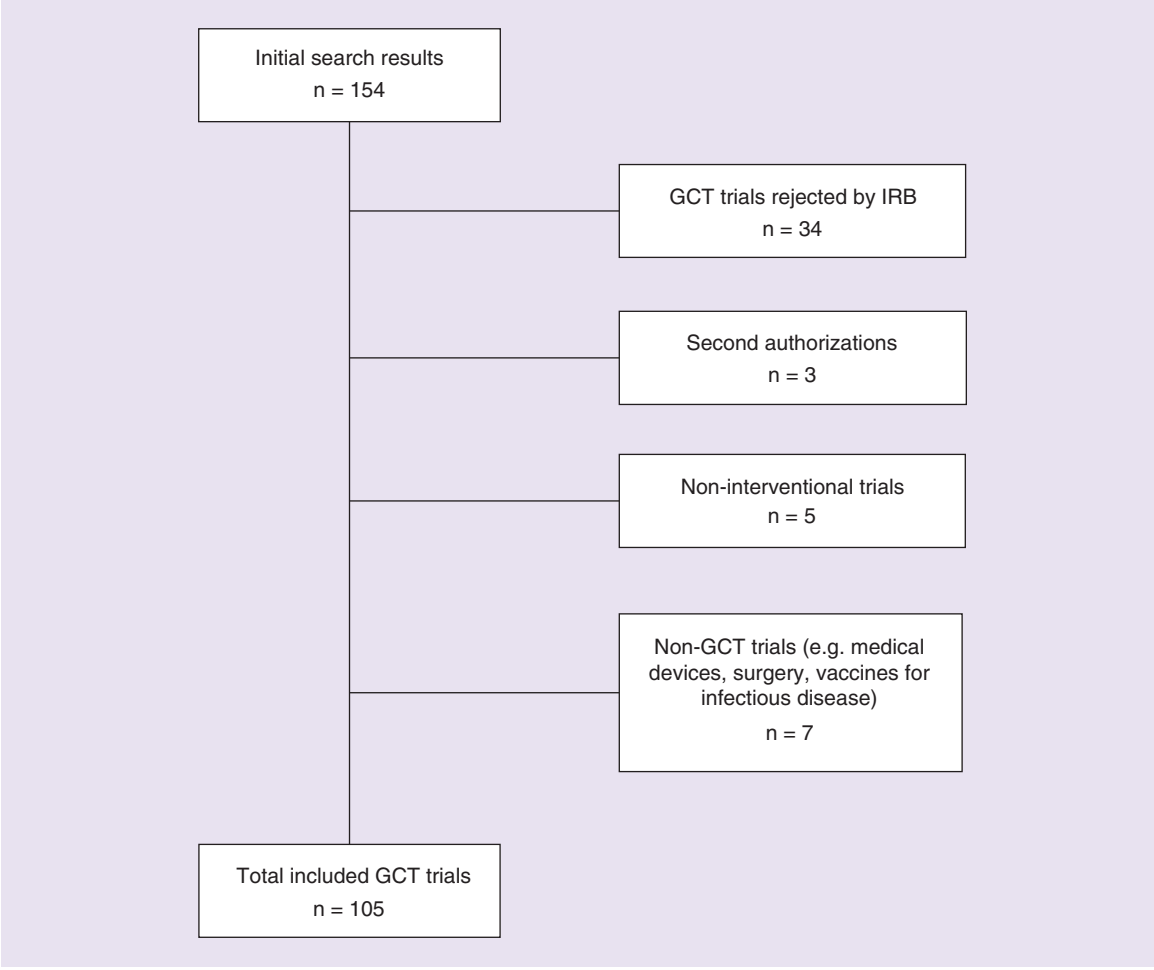

Figure 1. Selection of gene and cell-based therapy clinical trial cohort.
GCT: Gene- and cell-based therapies; IRB: Institutional Review Board.

published for trials that were authorized before 2014 (23/30 scientifically published trials), compared with trials authorized since 2014 (7/30 scientifically published trials). In contrast, publication through conference abstracts was comparable for trials authorized before 2014 (12/27 trials published at conferences) versus trials authorized since 2014 (15/27 trials published at conferences). There was little overlap between publication in scientific papers and conferences abstracts. Only for 8% of trials (n = 8/105), results were published in conference abstracts first and subsequently scientifically published (Figure 2). Of all conference abstracts, 30% was scientifically published (n = 8/27).

Reported knowledge

In total, 110 publications (scientific papers n = 40; conference abstracts n = 70) were found to match in total 49 out of 105 trials in the cohort. When stratifying publications by sponsor type, results show that most scientific papers were published from publicly sponsored trials (n = 33/40), compared with privately sponsored trials (n = 7/40). In contrast, relatively few conference abstracts were published from publicly sponsored trials (n = 13/70), compared with privately sponsored trials (n = 57/70; Figure 3).

Clinical safety and clinical outcomes on biomarkers or surrogate end points were reported in 70 and 78% of scientific papers, respectively. Clinical outcomes on clinical end points were reported in 58% of scientific papers. Overall, conference abstracts often reported clinical outcomes (90% – not shown). Clinical safety, clinical outcomes on biomarkers or surrogate end points and clinical outcomes on clinical end points were reported in 59, 54 and 37% of conference abstracts, respectively (Figure 3). In total, three scientific papers reported detailed manufacturing

Table 1. Frequencies, publication proportions and associations of trial characteristics with the outcome of scientific publication, expressed as crude hazard ratios with 99% CIs and p-values (n = 105).

Trial characteristic	Trials, n	Published, n (% published)	Not published, n (% not published)	Crude HR (99% CI)	p-value
All included GCT trials	105	28	77		
Sponsor					
– Academic hospital	56	23 (82%)	33 (43%)	2.1 (0.5–8.6)	0.17
– Other public sponsor	14	1 (4%)	13 (17%)	0.4 (0.02–6.4)	0.36
– Private sponsor	35	4 (14%)	31 (40%)	Ref	
Product type					
– Gene therapy	25	4 (14%)	21 (27%)	1.2 (0.3–4.7)	0.80
– Cell therapy	80	24 (86%)	56 (73%)	Ref	
Therapeutic area					
– Other disease areas	52	19 (68%)	33 (43%)	2.4 (0.8–6.7)	0.03
– Oncology	53	9 (32%)	44 (57%)	Ref	
Active substance[†]					
– Stem and other cells	49	14 (50%)	35 (46%)	Ref	
– Lymphocytes	21	6 (21%)	15 (20%)	1.3 (0.4–4.8)	0.55
– Dendritic cells	20	5 (18%)	15 (20%)	0.99 (0.3–3.8)	0.99
– Gene delivery vectors	15	3 (11%)	12 (16%)	0.97 (0.2–5.0)	0.96
Trial phase					
– Early phase (Phase I, I/II)	48	16 (57%)	32 (42%)	1.6 (0.6–4.4)	0.20
– Late phase (Phase II, II/III, III, IV)	57	12 (43%)	45 (58%)	Ref	
Randomized design					
– No	57	17 (61%)	40 (52%)	1.6 (0.6–4.2)	0.26
– Yes	48	11 (39%)	37 (48%)	Ref	
Center					
– Single-centered	46	20 (71%)	26 (34%)	2.2 (0.8–6.6)	0.06
– Multicentered	59	8 (29%)	51 (66%)	Ref	
Geographic location					
– Netherlands	58	23 (82%)	35 (46%)	1.9 (0.5–6.9)	0.19
– Multinational	47	5 (18%)	42 (54%)	Ref	

[†] Active substance refers to the component of a gene or cell-based therapy that is hypothesized to enact its mode of action.
GCT: Gene- and cell-based therapy; HR: Hazard ratio.

protocols and quality control methods. A small proportion of conference abstracts reported manufacturing and quality outcomes (9/70) (not shown).

Overall, 78% of publications included positive outcomes that supported further clinical development with the product. Negative results and suggestions for product alteration and/or new clinical research were reported in 9% of publications. The remaining publications entailed clinical trial protocols, without reporting of trial results (13%). Scientific papers mostly reported positive results (n = 29/40), whereas a smaller proportion reported negative results (n = 8/40) and no results (n = 3/40). Conference abstracts mostly reported positive results (n = 57/70), whereas a smaller proportion reported negative results (n = 2/70) and no results (n = 11/70) (not shown).

Scientific publication

The scientific publication rate is 27% of GCT trials (n = 28/105) (Table 1). The publication rate would be slightly higher without exclusion of publications before IRB authorization for Cox regression analysis (29% of trials; n = 30/105). The scientific publication rate for all GCT trials sponsored by academic hospitals is highest (41% of trials; n = 23/56 trials).

The univariate Cox regression analysis shows that trial results are more likely to be published for trials that were conducted in other disease areas than oncology, compared with oncology (crude HR: 2.4; 99% CI 0.8–6.7; p = 0.03). Furthermore, it is likely that results of single-center trials are scientifically published more compared with

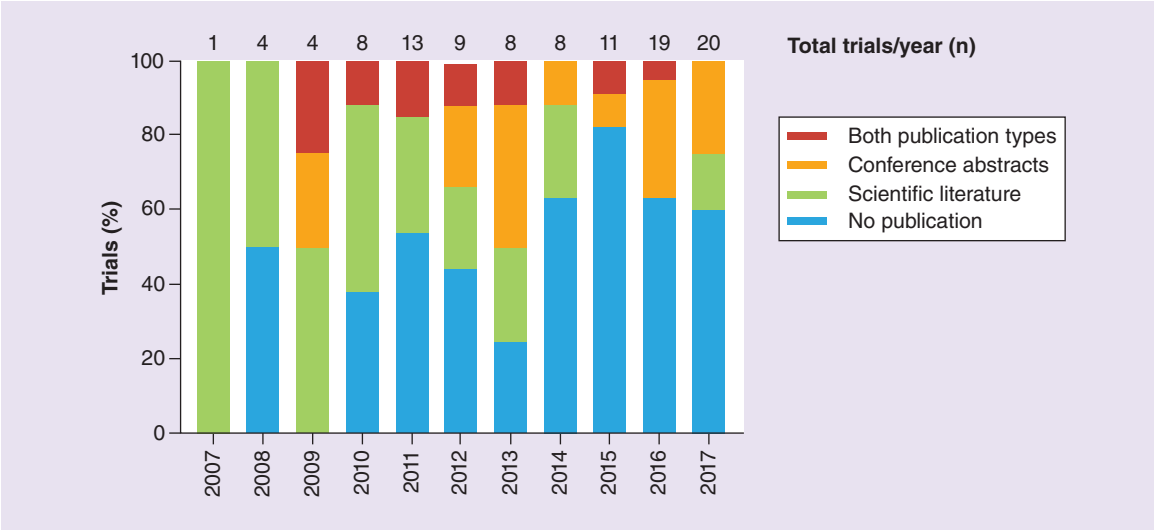

Figure 2. Year of trial authorization and outcome of publication. Percentage of trials that were published per year of authorization, stratified by publication outcome (no publication, publication in scientific literature, publication in conference abstracts or publication in both scientific literature and conference abstracts).

multicenter trials (crude HR: 2.2; 99% CI 0.8–6.6; p = 0.06). Yet, these associations are not significant. In addition, associations between sponsor, trial phase, randomized design and geographic location and the outcome of scientific publication are uncertain (p = 0.1–0.2) as well as the size of their potential association. Univariate analysis indicates no association between product type and active substance and the outcome of scientific publication (Table 1).

Conference abstract publication

The conference abstract publication rate is 17% of GCT trials (n = 18/105). The conference abstract publication rate would be higher without exclusion of publications before IRB authorization for Cox regression analysis (26%, n = 27/105). Most trials for which publications were excluded (n = 8/9) were multicenter, multinational trials, authorized in the Netherlands in 2016–2017 (n = 7/9) and sponsored by private entities (n = 7/9). All excluded publications were in the field of oncology.

The univariate Cox regression analysis shows that trial results are significantly less likely to be published in conference abstracts if trials were sponsored by academic hospitals, compared with privately sponsored trials (crude HR: 0.3; 99% CI 0.1–0.94; p = 0.01). It is less likely that trial results are published in conference abstracts for single-center trials, compared with multicenter trials (crude HR: 0.2; 99% CI 0.1–1.08; p = 0.014) and for national (Dutch) trials, compared with multinational trials (crude HR: 0.3; 99% CI 0.1–1.08; p = 0.015), although these associations approach significance. Furthermore, results suggest that GCT trials with lymphocytes as the active substance, compared with stem cells, are published more in conference abstracts (crude HR: 2.6; 99% CI 0.5–12.5; p = 0.11), although the effect size is uncertain and the association is nonsignificant. Univariate analysis indicates no association between product type, therapeutic area, trial phase, randomized design and the outcome of publication through conference abstracts (Table 2).

Discussion

The aim of this study was to provide insight into GCT publication rates, associations between publication and trial characteristics and which type of results are reported. Our cohort mainly consisted of academically sponsored, single-centered, national (i.e., Dutch) trials and privately sponsored, multicenter, multinational trials. These characteristics are similar to the characteristics of GCT trials conducted throughout the whole EU [19]. Results were either published in scientific papers (27% scientific publication rate) or conference abstracts (17% conference abstract publication rate). Results are indicative of more scientific publication by academic hospitals compared with private sponsors, whereas academic hospitals are less likely to publish results in conference abstracts compared with private sponsors. Detailed knowledge on manufacturing and quality outcomes was underreported

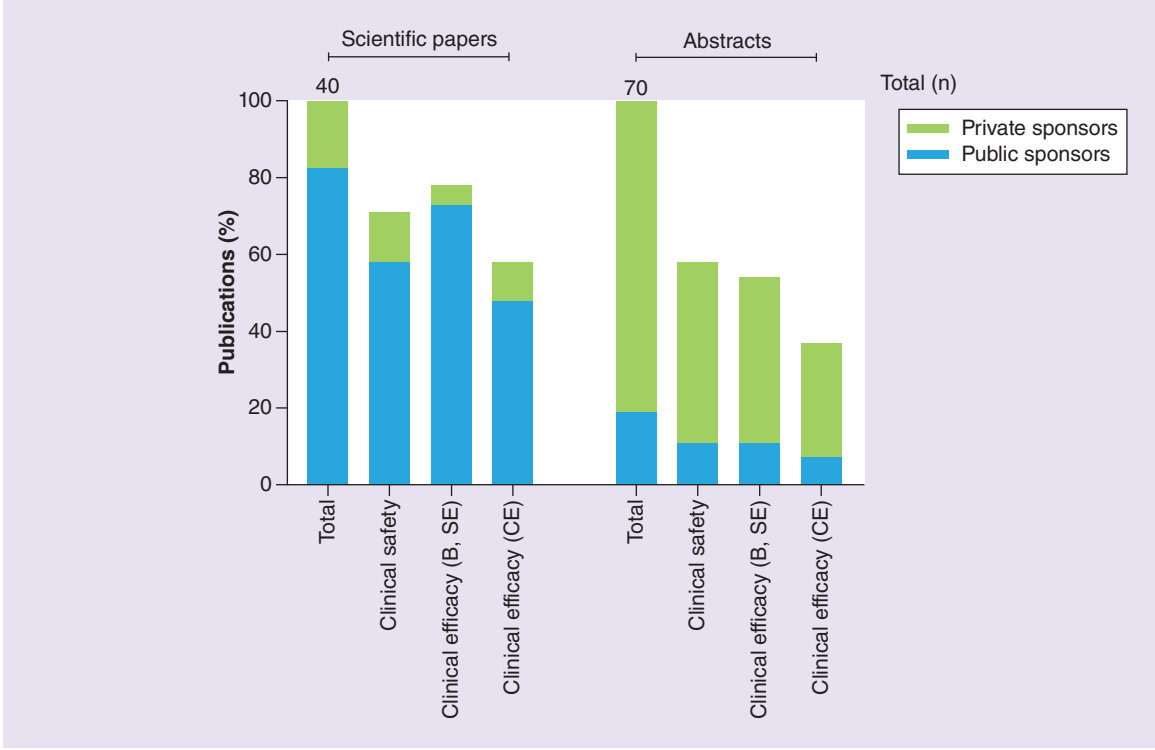

Figure 3. Proportions of clinical outcome reporting in publications, stratified by type of publication and public and private sponsors (n = 110). Publications frequently reported multiple categories of clinical knowledge. Therefore, the proportions reported under clinical safety, clinical outcomes of biomarkers or surrogate end points and clinical outcome on clinical end points do not add up to the total proportion of publications.
B: Outcomes reported on biomarkers; CE: Outcomes reported on clinical end points; SE: Outcomes reported on surrogate end points.

compared with clinical outcomes in scientific literature. Most publications reported positive outcomes and are suggestive of continued clinical development.

Our observations underline the important role of single-centred academic trials [27] to build up the GCT knowledge base. This is consistent with the important role of public sponsors in drug discovery in general, particularly in novel fields [32]. The scientific publication rate of 41% by academic hospitals is within range of earlier shown publication rates for clinical drug trials that were sponsored academic hospitals in USA [33]. In contrast, scientific publication by private sponsors is limited. A large proportion of private sponsors consist of small companies in our cohort, who struggle to comply with regulatory requirements and to complete development trajectories for marketing authorization [18]. Resources and priorities for scientific publication are probably limited within those firms. In addition, private sponsors may not publish because of intellectual property rights and other commercial considerations, similar to observations in the field of biotechnology [34]. For example, private sponsors face technological competition when bringing new products to the market that are based on the same collective knowledge base [28]. Therefore, it is important that small companies become more attentive to scientific publications considering their substantial role in the GCT field [18].

The scientific publication rate of 27% is likely to be influenced by short follow-up period for a part of the trials included in our sample. When restricting the analysis to trials with at least a median follow-up of 4.5 years, the publication rate increased to 49%. In addition, many of the trials authorized later in our cohort were multicenter trials. Previous work shows that followed up period of at least 8–9 years increase the likelihood of scientific publication for multicenter trials [8]. Considering the lengthy process of conducting large multicenter trials, it is very likely that the follow-up time in our study was insufficient to allow for publication of results from multicenter trials. However, the GCT field is relatively new, which limited us to design a methodology with extended follow periods. This is reflected in the limited number of trials in earlier years and high proportions of early phase trials in our cohort. In addition, there are other factors than trial authorization that influence publication such as

Table 2. Frequencies, publication proportions and associations of trial characteristics with the outcome of presenting results at conferences, expressed as crude hazard ratios with 99% CIs and p-values (n = 105).

Trial characteristic	Trials, n	Presented, n (% presented)	Not presented, n (% not presented)	Crude HR (99% CI)	p-value
All included GCT trials	105	18	87		
Sponsor					
– Academic hospital	56	7 (39%)	49 (56%)	0.3 (0.1–0.94)	0.01
– Public sponsor	14	1 (6%)	13 (15%)	0.2 (0.01–2.4)	0.08
– Private sponsor	35	10 (55%)	25 (29%)	Ref	
Product type					
– Gene therapy	25	5 (28%)	20 (23%)	1.9 (0.5–7.6)	0.23
– Cell therapy	80	13 (72%)	67 (77%)	Ref	
Therapeutic area					
– Other disease areas	52	8 (44%)	44 (51%)	0.7 (0.2–2.5)	0.50
– Oncology	53	10 (56%)	43 (49%)	Ref	
Active substance[†]					
– Stem and other cells	49	6 (33%)	43 (49%)	Ref	
– Lymphocytes	21	5 (28%)	16 (18%)	2.6 (0.5–12.5)	0.11
– Dendritic cells	20	4 (22%)	16 (18%)	1.8 (0.3–9.7)	0.35
– Gene-delivery vectors	15	3 (17%)	12 (14%)	2.2 (0.3–13.5)	0.28
Trial phase					
– Early phase (Phase I, I/II)	48	7 (39%)	41 (47%)	0.7 (0.2–2.5)	0.51
– Late phase (Phase II, II/III, III, IV)	57	11 (61%)	46 (53%)	Ref	
Randomized design					
– No	57	11 (61%)	46 (53%)	1.4 (0.4–4.8)	0.50
– Yes	48	7 (39%)	41 (47%)	Ref	
Center					
– Single-centered	46	4 (22%)	42 (48%)	0.2 (0.1–1.08)	0.014
– Multicentered	59	14 (78%)	45 (52%)	Ref	
Geographic location					
– Netherlands	58	7 (39%)	51 (59%)	0.3 (0.1–1.08)	0.015
– Multinational	47	11 (61%)	36 (41%)	Ref	

[†]Active substance refers to the component of a gene or cell-based therapy that is hypothesized to enact its mode of action.
GCT: Gene- and cell-based therapy; HR: Hazard ratio.

trial progression. For instance, early termination is an important determining factor for publication of drug trial results [8]. Further investigation is needed to investigate the impact of trial progression, as well as other measures of study quality [8,30], on publication of GCT trial results.

Despite these methodological limitations, our explorative Cox analysis contradicts previously reported associations between scientific publication and multicentered, late phase, oncology drug trials [8,35]. Results show a higher likelihood of scientific publication for other disease areas than oncology, which can be explained by substantial early GCT development for severe indications across therapeutic areas. Early phase GCT trials are typically directly conducted in patients, which is postulated to account for higher likelihoods of scientific publication [8]. This provides an explanation why we did not find previously reported associations between scientific publication and late phase trials in the field of oncology [8,35].

The publication rate of conference abstracts was found to be rather low (17%), which can partly be explained by the low publication rate of conference abstracts by academically sponsored trials. This is surprising and needs to be investigated further. Our results indicate publication through conference abstracts by private sponsors, which is encouraging. In addition, many recent events of conference publication had to be excluded from analysis for multicentered, multinational trials because knowledge of other sites had been shared before trial authorization in the Netherlands. These trials are illustrative of successful commercial developments in the GCT oncology field, most evidently with T-cell therapies to target malignancies [36–38]. Without excluding these trials, the publication

rate of conference abstracts would have been higher but still suboptimal (26%). Therefore, to fully understand publication rates of multicentered trials, larger cross-country cohort studies are needed in order to capture initial trial authorization. Furthermore, full peer-reviewed reporting can only be achieved through scientific publication [39]. Previous work shows that 20–33% of published conference abstracts are thereafter published in scientific papers [39–41], which is consistent with the percentage of abstracts that were later scientifically published found here. Publication of trial results through conference abstracts may be part of strategies to maximize commercial value of available scientific data, with potential knowledge biases [42]. Therefore, it is important that private sponsors continue to share their GCT trial results after publishing conference abstracts.

The novelty of the GCT field and the limited knowledge base may, in itself, account for the rather limited publication rates. The high rejection rate of 24% of GCT trial applications shown here, in comparison to a rejection rate of 3% in a cohort of Dutch IRB-authorized drug trials [30], underlines translation difficulties from preclinical to clinical testing [43]. Challenges to translate *in vivo* results from animal studies to humans can result in clinical trial failure, which may explain the high rate of nonpublication here due to publication biases [11–14]. Limited biological understanding of GCT interactions in humans is illustrated by the high reporting of findings based on biomarkers or surrogate end points. Other previously reported factors for nonpublication include having other priorities and rejection by journals [8,44,45]. Journals may be more inclined to accept results of late phase trials conducted with pharmaceuticals, forcing sponsors of early phase trials that study niche GCT technologies to compete for limited publication space in specialized journals. Moreover, our results indicate that most GCT publications entailed positive results. Considering reports of a publication bias toward positive clinical outcomes for drug trials [11–14], it is likely that such a publication bias exists for GCTs as well. However, clinical trials registers provide another destination for publication of trial results, including those for early terminated or failed trials. Before data collection, we defined publication of trial results in EudraCT as an outcome measure. However, results were reported in EudraCT for only two trials in the cohort and were excluded from methodology due to this limited count of events. This is rather surprising as publication of trial results in registries is required within 12 months after trial completion [46]. It clearly underlines earlier reports that result reporting in clinical registries is not standard practice and needs to be improved [33,47].

Currently, quality and trial design standardization remain complicated due to relatively limited clinical experience and heterogeneity of different GCT technologies. Publication is one of several strategies to enhance learning among academia and to facilitate collaboration with industry. Collaboration can be achieved through development in public–private partnerships, engagement in license agreements or spinning off small companies that are later acquired by large industry [48–50]. The proportions of technological know-how reporting shown here probably do not suffice to increase the knowledge base on manufacturing and quality and to work toward standardized manufacturing protocols. Therefore, there is a need for increased sharing of knowledge on key quality attributes among researchers, either through publication or collaboration. This includes large-scale initiatives for pooling of knowledge on manufacturing and quality to facilitate standardization of manufacturing protocols as was recently done for mesenchymal stromal cells [51]. Furthermore, it is paramount that GCT developers carefully develop in-process and release specifications to prevent objections by regulators in later development stages [52] or failures to transfer technology to industry [53]. Innovative medicines that reach marketing authorization are traditionally transferred to industry after successful early clinical development [50,54], of which transfer or partnering with large industry is most successful [55]. If public GCT trial sponsors prefer to commercialize their products, it is crucial to establish target product profiles and joint services to streamline collection of patient material, manufacturing and distribution efforts [27].

A strong collective knowledge base is critical to ensure technical and clinical information synthesis in new fields [34]. Due to the large proportion of local clinical activities, this is particularly relevant for the GCT field [19,27]. Publication rates in scientific literature and conference abstracts are currently suboptimal in the novel GCT field. If trial completion increases and developers become more attentive to publication over time, publication rates could increase. Enhanced publication of GCT trial results in the near future would facilitate mutual learning in the field and is instrumental in making GCT development more open and collaborative [56,57].

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/rme-2019-0066

Author contributions

Conceptualization was performed DGM Coppens, H Gardarsdottir, CA van den Bogert and J Hoekman; methodology was performed by DGM Coppens, H Gardarsdottir and J Hoekman; investigation was performed by DGM Coppens and H Gardarsdottir; DGM Coppens, H Gardarsdottir and J Hoekman wrote the original draft; review and editing was performed by H Gardarsdottir, CA van den Bogert, ML De Bruin, HGM Leufkens and J Hoekman. Supervision was performed by H Gardarsdottir, ML De Bruin, HGM Leufkens and J Hoekman.

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Summary points

- Timely publication of trial results is essential to advance gene- and cell-based therapy (GCT) development.
- We constructed a clinical trial cohort consisting of 105 authorized GCT trials in the Netherlands (2007–2017) and searched for publications of these trials until 1 July 2018.
- A total of 110 publications (scientific papers n = 40; conference abstracts n = 70) were found to match in total 49 trials in the cohort.
- After a median survival time of 1050 days since GCT trial authorization, the scientific publication rate was 27% and the conference abstract publication rate was 17%.
- The scientific publication rate for all GCT trials sponsored by academic hospitals is highest (41%). Trial results show a trend of more scientific publication for trials that were conducted in other disease areas than oncology compared with oncology and for single-center trials compared with multicenter trials.
- Single-center trials and trials sponsored by academic hospitals were significantly less likely to be published in conference abstracts compared with multicenter and privately sponsored trials.
- Detailed knowledge on manufacturing and quality outcomes was underreported compared with clinical outcomes.
- Most publications (78%) report positive outcomes and suggest continued trial conduct.
- Publication rates in scientific literature and conference abstracts are currently suboptimal in the novel GCT field, yet these may improve over time.

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