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Extent of and reasons for discontinuation and nonpublication of interventional trials on connective tissue diseases: an observational study.

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Abstract

Objectives. To assess the proportion, the reasons, and the factors associated with discontinuation or nonpublication of randomized controlled trials (RCTs) on connective tissue diseases (CTDs).

Methods. We searched all interventional RCTs on CTDs registered in Clinicaltrials.gov since 2000. Two reviewers selected studies according to pre-specified eligibility criteria. Completion status, publication status, reported reasons for discontinuation or nonpublication, were retrieved on Clinicaltrials.gov, through literature search, and by contacting investigators. Multivariable logistic regression was used to identify factors associated with study noncompletion and nonpublication.

Results. We included 175 studies, mostly phase 3, placebo-controlled trials on pharmacologic treatments, recruiting patients with systemic lupus (51%), systemic sclerosis (20%), Sjögren syndrome (12%) or other CTDs. Fifty-eight (33%) had been discontinued, mainly for insufficient patient accrual, with no differences in discontinuation rates across the CTDs (P>0.5). Forty-six (35%) of 130 studies having included at least 1 patient resulted unpublished, and 86 (65%) were published in a peer-reviewed journal after a median of 24 months (IQ 15-41) from completion, with a significant higher publication rate in completed vs. discontinued studies (81% vs 22%; P<0.001). We were able to obtain reasons for nonpublication in one-third of cases. Small sample size (< 100 participants) was the only factor associated with study noncompletion and nonpublication.

Conclusions. One of three registered CTD-RCTs fails to be completed or published. This represents a waste of resources and raises ethical concerns regarding hidden clinical data and unfruitful participation by patients.

Significance and innovation

- Trial discontinuation and nonpublication represent a waste of resources and raise ethical concerns regarding hidden clinical data and unfruitful participation by patients.

- One of three CTD-RCTs registered after 2000 failed to be completed or published, with similar rates recorded across CTDs.

- Smaller studies were more likely to be either discontinued or unpublished.

- A better understanding of the factors leading to study failure will guide future allocation of resources and could help to maximize the successful conduct of RCTs.

Introduction

Connective tissue diseases (CTDs) are systemic autoimmune diseases, some of which rare, characterized by a dysregulated immune response and heterogeneous clinical picture (1, 2). Although the knowledge of their pathogenesis has improved over the past years, patients with CTDs are still burdened by high disability, impaired quality of life and poor survival. For some CTDs manifestations, we currently have treatments with no or very limited proven efficacy. For example, the immune-related destruction of exocrine glands in Sjögren syndrome (SJO) (3), or the accumulation of fibrosis in skin and inner-organs of systemic sclerosis (SSC) patients (4) are poorly responsive to currently available drugs. The rate of complete remission after therapy for severe lupus (SLE) nephritis is still disappointingly suboptimal (5). It is therefore a priority to obtain robust evidence of treatment efficacy through randomized controlled trials (RCTs) in these diseases where treatment options are scarce.

However, the achievement of this goal can be hindered by trial failure or by nonpublication of study results. Trial discontinuation not due to valid ethical and scientific reasons, and nonpublication of RCTs results are major issues for the advancement of medical knowledge (6-8). The failure to complete a trial is a waste of time and money, and a missed opportunity to contribute to patient's health (7). It is also unrewarding for patients who volunteer to participate against the risks of receiving no benefit or to being exposed to harms, with potential difficulties to involve them in future studies. Aside from ethics and conduct issues, nonpublication of study results leads to publication bias that can undermine the validity of systematic reviews or meta-analyses (9).

In other medical fields, discontinuation and nonpublication of RCTs have been identified as common problems (10-14), preventable in many cases (15, 16).

Currently, this issue has not been addressed for CTDs. We therefore designed this study to determine how frequently RCTs on CTDs terminated early or didn't reach

publication; describe the underlying reasons; and identify risk factors for early study termination or nonpublication.

Search strategy

On 19 March 2021 we searched for CTDs-RCTs registered before this date on ClinicalTrials.gov, and having started after 01.01.2000 (ClinicalTrials.gov began registering trials in 2000). We used the advanced search function on ClinicalTrials.gov to identify the diseases of interest within the 'Immune system disease' and 'Skin and Connective Tissue diseases' categories. We included studies on CTDs encompassing Undifferentiated connective tissue disease (UCTD), Systemic sclerosis (SSC), (systemic) Lupus erythematosus (SLE), Sjögren syndrome (SJO), Dermatomyositis/Polymyositis/Inclusion body myositis (DM/PM/IBD), Mixed connective tissue disease (MCTD), and Antiphospholipid syndrome (SAPS). The complete list of keywords used for the search is in the online supplementary file. Trial entries provide details on the study population, intervention type, start and completion dates, funding source, design characteristics, and current recruitment status. The retrieved results were then downloaded, and uploaded in R 4.1 statistical software (R Development Core Team, Vienna, Austria) for analysis.

Study eligibility criteria

We included only interventional randomized trials (phase 2/3, 3 or 4) with a completed, suspended, terminated, withdrawn, or unknown status, as defined in Clinicaltrials.gov glossary (online file). Studies labeled as completed formed the 'Completed' group, those reported as terminated, withdrawn, suspended formed the 'Discontinued' group. The studies whose status was considered unknown, were included among the 'Discontinued' or 'Completed' ones, according to whether results were posted on Clinicaltrials.gov or a related peer-reviewed publication was found by direct search or author query (see 'Contacting authors' paragraph). We excluded non-randomized studies, RCTs with another status (i.e. recruiting, not yet recruiting, etc.), or not targeting a CTD, as well as duplicated studies.

Definitions and data characterization

The following study characteristics were retrieved and analyzed: funding sources (industry, non-industry), planned sample size, study design (i.e., parallel-arms, cross-

over), type of intervention (pharmacologic, non-pharmacologic), type of comparator (placebo, active intervention, usual care, or no intervention), time to primary outcome. A study was considered being industry-funded if industry was the sponsor or one of the collaborators (an organization other than the sponsor providing support for a clinical study), as reported in the glossary of Clincaltrials.gov. We classified trials as international if conducted in more than one country. Reasons for trial noncompletion were extracted from ClinicalTrials.gov, or if not available or in case of unclear reasons, we contacted by mail study investigators and/or sponsors to obtain additional information as detailed below (see 'Contacting authors' paragraph).

Publication search

Two authors (MI, AB) reviewed Clinicaltrials.gov to identify the publication status of each included trial. If a link for a publication was available, it was checked for consistency. In case of lack of information about publication status, we searched PubMed, Scopus and Google Scholar for national clinical trial (NCT) numbers, title, authors, or intervention. For industry-funded trials, we also searched company websites. Publication status was checked only in trials completed before January 1st, 2017 because we allowed the included trials more than 48 months from the latest completion date (January 1st, 2017) to the time of our search (March 19th, 2021), in order to exclude publication delay due to COVID-19 pandemic. A RCT was defined as 'published' only if results were delivered in a peer-reviewed journal in the form of a complete manuscript, even if catalogued in print or in press. We made this choice since the peer-review process should ensure that trial's results are thoroughly checked for scientific validity and clarity. We also recorded if the study results were posted in Clinicaltrials.gov. We reviewed the full-text of identified publications to ensure a match with the respective Clinicaltrials.gov entry. The publication status was independently checked by 2 of the authors (MI, AB), and disagreement was solved by discussion with a third reviewer (BR). Time to publication was the interval between the primary completion date and the e-publication date of the related peer-reviewed manuscript. Completion date was used if primary completion date was lacking.

Contacting authors to obtain information on completion/publication status and/or on reasons for discontinuation/nonpublication

When reasons for trial discontinuation were not specified (for discontinued studies), or when we did not find any publication, we attempted to contact by mail the investigator(s) identified in Clinicaltrials.gov as 'Contact' or 'Corresponding author'. We used the mail address provided in ClinicalTrials.gov, or if unavailable, we searched in her/his institution website, in PubMed publications, et finally in Google. Once a mail address obtained, we sent a standardized mail used in previous papers (12, 17) to ask for completion/publication status, and relative reasons for noncompletion or nonpublication (online file). A reminder mail was planned after 2 weeks. In case we didn't receive any response within 8 weeks or the email was returned as inactive, we considered the author uncontactable. Trial was considered unpublished if both the search process and email contact did not provide evidence of publication in a peer-reviewed journal.

Statistical analysis

Trial's characteristics are reported as the number (percentage) for categorical variables or median [inner quartiles; IQ] for continuous variables. Continuous variables were compared with Student's t-test or Mann–Whitney test, and categorical variables with chi-square test or Fisher's exact test, as appropriate. False discovery rate (FDR) was used to correct for multiple comparison. We used logistic regression models to assess the impact of variables previously shown to impact trial completion and publication (6, 11, 18), e.g. the disease, study phase, planned sample size (≥100 versus <100 patients) for discontinuation and nonpublication, plus intervention type (pharmacologic vs. non-pharmacologic) for discontinuation (6, 11, 18). The binary outcome targets were firstly discontinuation (versus completion) and secondly publication (versus nonpublication). All statistical analyses were computed with R v4.1; $p \leq 0.05$ was considered significant. Ethical approval was not required (study not involving human participants).

Results

Among the 1,191 RCTs identified (flow-chart shown in Figure 1), we included 175 studies of which 117 (67%) were identified as completed, and 58 (33%) as discontinued (Figure 2). Studies were mostly phase 3, placebo-controlled trials testing pharmacologic treatments, most of which conducted in North America (n=70; 40%), investigating SLE (n=90; 51%), and potentially enrolling up to 36,594 patients in total.

Half of RCTs were industry-funded. Table 1 provides further details regarding trial characteristics. The median planned sample size was of 101 patients (IQ 51-250), with 83 RCTs (47%) aiming to recruit less than 100 patients.

Discontinuation

The 58 discontinued trials [withdrawn (n=12; 21%), terminated (n=33; 57%), unknown status (n=13; 22%)] could have potentially enrolled 11,389 patients, representing 31% of the estimated number of CTD patients planned to be investigated among all studies. They effectively recruited 6,242 patients (5,075 SLE, 714 SSC, 132 APS, 14 SJO, 1 PM/DM, 306 more than a CTD). Discontinuation rate was 41% for SLE, 28% for SSC, 9.5% for SJO, 18% for PM/DM/IBM trials (P=0.22).

Contact emails were identified for 18 of 20 discontinued trials (90%) that did not indicate a reason for discontinuation, and answers were received for 3 of 18 emails (17%). After email responses, reasons for trial discontinuation were available for 39 of 58 trials (67%) and included insufficient patient accrual (n=11), interim study results indicating futility (n=8), safety concerns (n=5), funding issues (n=5), conduct problems (e.g., pharmacy unwilling to comply with study protocol) (n=4), company decisions (n=2), administrative reasons (n=2), principal investigator departure (n=1), or unclear (n=1)(19). Trials discontinued for poor recruitment (n=11) achieved a median percentage of target sample size of 1.2% (IQ 0%-13.3%), were not collaborative international RCTs in most cases (n=9), and aimed to test interventions for SLE (n=9). By subtracting from the 58 discontinued trials the 13 studies for which early termination was justified (e.g. discontinuation for futility or safety concerns), we considered 45 (26%) trials prematurely terminated.

Completed studies were less likely than discontinued studies to have a placebo arm as comparator, and their planning time for primary outcome evaluation was longer (Table 1). Multivariable logistic regression identified a sample size <100 as the only factor associated with early termination (OR 2,13, 95%CI 1,0 - 4,7; P = 0,05).

Publication

After having excluded studies that had not included any patient (‘withdrawn’, n=12), or those with a completion date after 1st January 2017 (n=12), the publication status was checked in 94 completed and 36 discontinued RCTs, for a total of 130 studies. By our initial search, we identified 46 unpublished studies, of which 26 (56%) contact mail

addresses were obtained and investigator contacted. We received 9 (35%) responses permitting us to confirm the unpublished status for 4 studies, and identify an additional published study. In 4 cases, authors' reply was not informative.

Summarizing information from internet searches and investigator's replies, we finally identified 44 (34%) unpublished studies, and 86 (66%) study published in a peer-reviewed journal after a median of 24 months (IQ 15-41) from study completion, with a significant higher publication rate in completed vs. discontinued studies (n=78; 81% vs n=8; 22%; P<0.001). Nine (25%) discontinued studies had their results only posted on Clinicaltrials.gov. A full publication was reported for 2 of 6 RCTs terminated for futility, 3 of 5 discontinued for safety concerns. Nonpublication rate was 32% for SLE, 31% for SSC, 29% for SJO, 44% for PM/DM/IBM trials (P=0.5). When available, main reasons for nonpublication were: study discontinued for poor recruitment (n=5), paper rejected and under preparation/review for another attempt of submission (n=3), lack of time (n=3), low priority (n=1), study ongoing (n=1). Table 1 shows trial characteristics according to publication status. Published versus nonpublished trials were more likely to be international, had a higher estimated sample size, and more commonly a placebo arm as comparator (Table 1). Multivariable logistic regression identified a sample size <100 as the main barriers to reach publication for completed studies (OR 0,15, 95%CI 0,03 - 0,6; P < 0,01). Figure 3 shows the included studies and their planned sample size grouped according to the disease, the completion and the publication status.

Discussion

Herein we show that about a third of interventional randomized studies on CTDs terminated early, mainly for difficulties in patient recruitment, with smaller studies more likely to be prematurely discontinued. Similarly, 1 in 3 trials never reached publication, among which 1 in 5 of those that completed the planned recruitment, and 4 in 5 of RCTs being discontinued after having enrolled at least one participant. Reasons for nonpublication were less commonly acknowledged or made publicly available by principal investigators. RCTs with smaller planned sample size, investigating nonpharmacological interventions, or those that had been discontinued were more likely not to be published. We did not observe any difference in noncompletion and nonpublication rate according to the disease, the geographical origin of the principal investigator and the funders.

Trial discontinuation, a major issue in clinical research, has been examined across different specialties, but never in CTDs. We found that this phenomenon concerns CTDs as much as other diseases, where its observed point prevalence ranges on average from about 10% to 35% (10, 12, 20). For instance, previous studies have estimated that about 10% of cardiovascular trials (10), 20% of trials conducted in children (13) or testing surgical treatments (11) have been discontinued, as well as about 30% of those recruiting patients with rare diseases (19) or head and neck malignancies (12). Consistent with data from other specialties (6, 13, 19, 21), insufficient patient recruitment was the main barrier to complete trials in CTDs. Interestingly, this issue mainly involved RCTs on SLE, the most frequent CTD, suggesting that factors other than disease prevalence can impair patient recruitment. Advocated reasons are various and complex to investigate, among which the use of too strict inclusion criteria, or the lack of international collaborations as well as patient's related features (22) as the leading ones. The need for a network approach in conducting CTDs trials, where multiple sites - including private practice - and patients themselves are actively involved, is being discussed by experts in the field (23). Strategies to make patients aware of the importance to participate in clinical trials, to better manage expectations and fears about RCTs participation, new ways to deliver trial information (i.e. social networks) or intervention (at patient's home), and finally a direct involvement of patients in trial teams, are some of the topics under study that could be instrumental to incentivize CTDs patients to take part in RCTs (23).

The second most frequent reason for study discontinuation (1 in 5 noncompleted RCTs) was the demonstration of lack of efficacy (futility) or safety concerns for the intervention(s) tested. This occurred for example in studies on ocrelizumab (24) and atacicept in SLE (25), stopped for excess of adverse events in interventional arms. The trial comparing rivaroxaban vs warfarin for patients with antiphospholipid syndrome was stopped for lack of benefit (26). We must underline, however, that early termination does not represent a waste of resources in these cases, but is highly informative and reflects the decision not to pursue patient's recruitment after a thorough evaluation of the risk/benefit ratio by data and safety monitoring boards. Findings from these RCTs must therefore be rapidly disseminated to inform future research programs and clinical care. Unfortunately, this is not always the case. Actually, we observed that about half of CTD trials terminated for futility or safety were

never published. This raises practical and ethical concerns and represents a major problem in research (7).

In line with results from other medical fields (11, 13, 14, 19), we found that 1 in 3 studies on CTDs were unpublished. The nonpublication represents a violation of the obligation to disseminate knowledge about the results involving human subjects (regardless of study findings) (27, 28), introduces publication bias, and may produce other potentially deleterious effects such as waste of limited resources, patient disincentive to participate in trials, and unnecessary study duplication (7, 29). Although any dissemination of results is valuable, we considered as 'published' only studies appearing in a peer-reviewed journal. The peer-review process should ideally ensure that trial's results are thoroughly checked for scientific validity and clarity, and permit to distinguish high -quality research from that conducted with questionable methodology whose findings are increasingly disseminated through social networks, media, or pre-print repositories (30). Furthermore, even when made publicly available in ClinicalTrials.gov, study results are often difficult to interpret because of the lack of information about the methodology used, the hypotheses tested, and the statistical significance of the findings.

Nonpublication could be justified in some instances by valid reasons (e.g. manuscript in preparation, no patient recruited), but data from the literature suggest that it mostly arises from the failure of authors to write up and submit their work, mainly for disputable reasons, including negative study results (29). For CTD trials, failure to publish was mostly due to poor patient recruitment, lack of time, low priority, or attempt to resubmit study results after rejection by journals. This last aspect seems to be, however, less relevant since reported in only a few CTD-RCTs. Such finding aligns with data in the literature suggesting that under-reporting of research reflects under-submission more than editorial rejection (31). However, although it is not likely to be the main cause, the tendency of editors to accept more studies with 'positive' results is another questionable behavior that could have contributed in part to the observed nonpublication rate (32).

It is necessary to mention also a variety of other difficult to investigate reasons that have shown to be related to an unsuccessful (or delayed) publication outcome (33, 34), and that could have partly explained, again, our findings. We refer to potential principal investigator's conflict of interests, both financial or related to his/her beliefs or

to his/her previous ‘academic’ findings (33, 34); or sponsor/funder reluctance to deliver negative results or finding raising safety concern about their tested interventions (33, 34).

As shown in other studies on the topic, many of the above-mentioned issues are preventable, and a better awareness of this aspect in the phase of study conception and implementation could maybe (15) help to develop strategies to minimize this problem. Moreover, initiatives providing a potential solution to nonpublication, like RIAT (Restoring Invisible and Abandoned Trials), where researchers with unpublished trials offer the opportunity to independent investigators to become ‘restorative authors’, should hopefully be promoted also among researchers investigating CTDs (35).
We should however underline that despite our efforts, we were able to know the reasons for nonpublication in only one-third of cases. This raises issues of transparency.

Another important point that deserves attention is the way to make results of discontinued trials publicly available. Where it is already difficult to get completed trials published, this becomes a major or insurmountable hurdle for incomplete studies. Efforts should be done to allow researchers to easily publish their incomplete trial data, for example in a dedicated online repository.
Smaller studies were more likely to be either discontinued or unpublished. An explanation can be found in the intrinsic vulnerability of those RCTs being conceived and performed without the support of a broad network capable to assure achieving the goal of a peer-reviewed publication (sufficient funding, multiple recruiting centers, experienced investigators, etc). As observed for discontinuation, also the nonpublication rate was similar across the different CTDs.

The role of funders in RCTs completion and publication varies across different diseases (6, 10, 13, 14, 19). The observed lack of influence of funding source on these outcomes in our sample mitigates the concerns about the advocated higher failure rate of academic-led trials due to an overoptimistic approach to recruitment and/or to difficulties to get sufficient funds (6, 10, 13, 14, 19, 36).

Our study was not conceived to explore in detail the questions remaining unanswered in CTDs field, but it can provide useful insights. Study termination hampered improving our knowledge on the efficacy of some drugs for lupus nephritis such as rituximab (NCT01673295, NCT01765842), abatacept (NCT01714817) or TNF-alpha blockers (NCT00368264); or if wearing night splints for hands could ameliorate disability of SSC patients (NCT01586663). Results on the potential benefit coming from a neuro-electrostimulator of the submandibular and sublingual salivary glands in Sjögren's syndrome have not been delivered yet (NCT01174329).

Our study has several limitations. Selection bias can arise from the inclusion of trials only from Clinicaltrials.gov. However, study results concerning Europe and Americas can be considered as representative of all registered trials recruiting from these continents (37). Moreover, we were not able to explore the role of factors potentially influencing trial completion (e.g. study complexity, characteristics of intervention), or of those factors well known to impact on publication (e.g. negative results) because they were not available in the online platform. Finally, we can't exclude that we have missed some publications associated with the included studies.

There is an urgent need to identify efficacious treatment for CTDs. The failure to complete RCTs represents not only a waste of energy or resources, but negatively impacts on patient's health. A better understanding of the factors leading to waste will guide future allocation of resources and could help to maximize the successful conduct of RCTs. Studies with larger patient numbers were more likely to be completed and published, so investment in their delivery is advisable. Further research is necessary to determine the optimal interventions to minimize the waste of time and resources due to trial noncompletion and nonpublication.

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Conflict of interest. The authors declare no conflict of interest.

Ethics approval. Not needed.

Contributors

AB, BR, DSC, MI contributed to planning and data collection, data quality control, data analysis, and interpretation. They drafted and revised the manuscript critically for important intellectual content and gave final approval of the version to be published. DM, KL, DA contributed to data collection, data quality control, reviewed the

manuscript, and provided important intellectual content. AB and MI had full access to the study data. All authors have read, revised, and approved this manuscript and had final responsibility for the decision to submit for publication.

Data sharing

Data collected will be made available following publication. Requests for data can be made to the corresponding author, outlining specific data needs, analysis plans and dissemination plans.

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Tables

Table 1. Characteristics of included studies according to their completion status.

	Completed N=117	Discontinued N=58	P	Unpublished N=44	Published N=86	P
Disease			0.23			0.76
Systemic lupus erythematosus	53 (45)	37 (64)		21 (48)	46 (53)	
Systemic sclerosis	26 (22)	10 (17)		8 (18)	18 (21)	
Sjögren syndrome	19 (16)	2 (3)		4 (9)	10 (12)	
Polymyositis/dermatomyositis/IBM	9 (8)	2 (3)		3 (7)	5 (6)	
More than one CTDs	8 (7)	5 (9)		7 (16)	5 (6)	
Antiphospholipid syndrome	2 (2)	2 (3)		1 (2)	2 (2)	
Continent of the PI			0.88			0.86
Africa	3 (3)	0 (0)		1 (2)	1 (1)	
Asia	25 (22)	12 (24)		7 (17)	15 (19)	
Central and South America	11 (10)	4 (8)		5 (12)	7 (9)	
Europe	25 (22)	11 (22)		11 (27)	16 (20)	
North America	47 (42)	23 (46)		17 (41)	41 (51)	
					47 (55)	
Industry-funded	59 (50)	31 (53)	0.88	21 (48)		0.76
International	38 (34)	13 (25)	0.74	8 (19)	35 (43)	**0.05**
Pharmacologic treatment	107 (91)	51 (89)	0.88	37 (84)	81 (95)	0.15
Comparator			**0.05**			**0.02**
Active	26 (22)	28 (48)		18 (44)	17 (20)	
No intervention	3 (3)	1 (2)		2 (5)	1 (1)	
Placebo	81 (69)	28 (48)		19 (46)	66 (78)	
Unknown	4 (3)	0 (0)				
Usual care	3 (3)	1 (2)		2 (5)	1 (1)	
Time to primary outcome, months				12 (4-12)	6 (3.5-12)	0.81
mean, SD	7 (3-12)	12 (6-19)	**0.04**			
Phase			0.88			0.76
Phase 2/3	18 (15)	11 (19)		11 (25)	14 (16)	
Phase 3	68 (58)	35 (60)		25 (57)	55 (64)	
Phase 4	31 (26)	12 (21)		8 (18)	17 (20)	
Design			0.34			1.00

Crossover	13 (11)	2 (3)		4 (9)	9 (10)	
Factorial	2 (2)	0 (0)		1 (2)	1 (1)	
Parallel	101 (86)	55 (95)		39 (89)	76 (88)	
Unknown	1 (1)	1 (2)		-	-	
Planned sample size, n, median (IQ)	101 (51-250)	85 (43-289)	0.47	61.5 (39-205)	137 (72-307)	**0.03**
Planned sample size < 100	53 (46)	30 (52)	0.87	28 (64)	29 (34)	**0.02**

Data are expressed as number (percentages), if not otherwise specified. **IBM**, Inclusion body myositis; **CTDs**, Connective tissue diseases; **PI**, principal investigator; **SD**, standard deviation; **IQ**, inner quartiles.

Figure 1. Flow-chart of study selection. Values are the number (percentage) of trials.

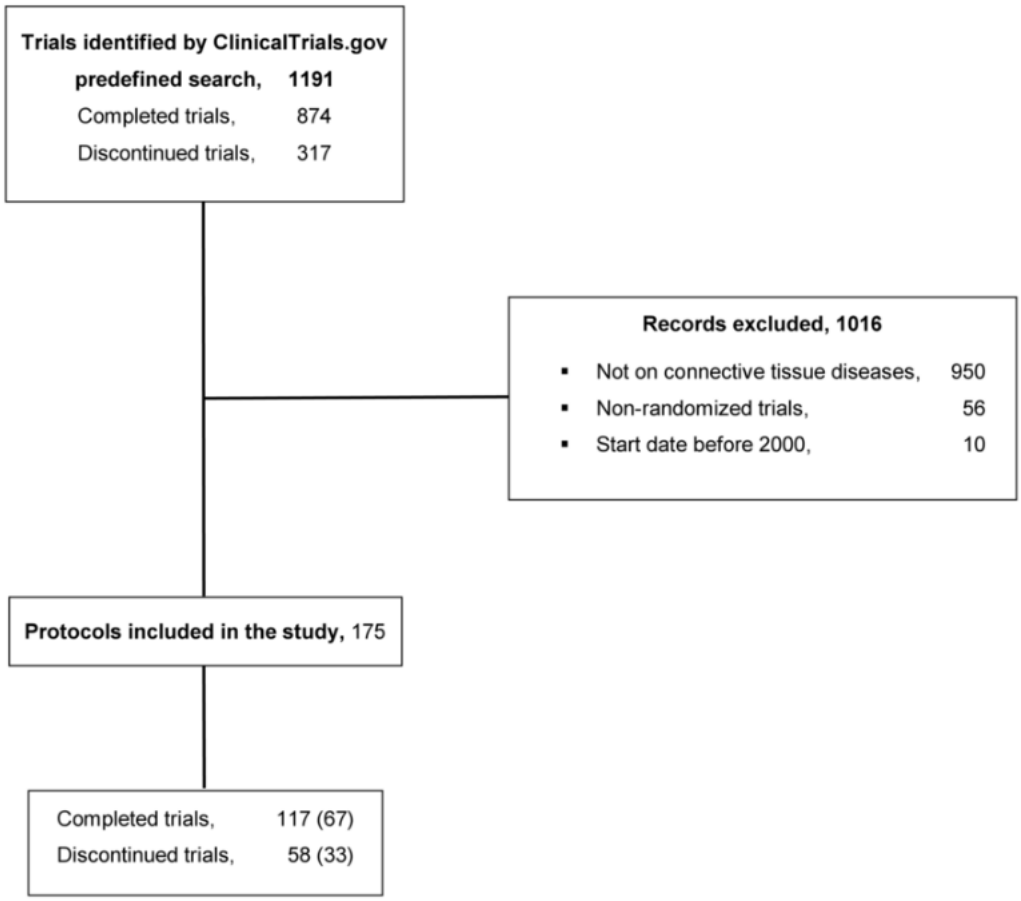
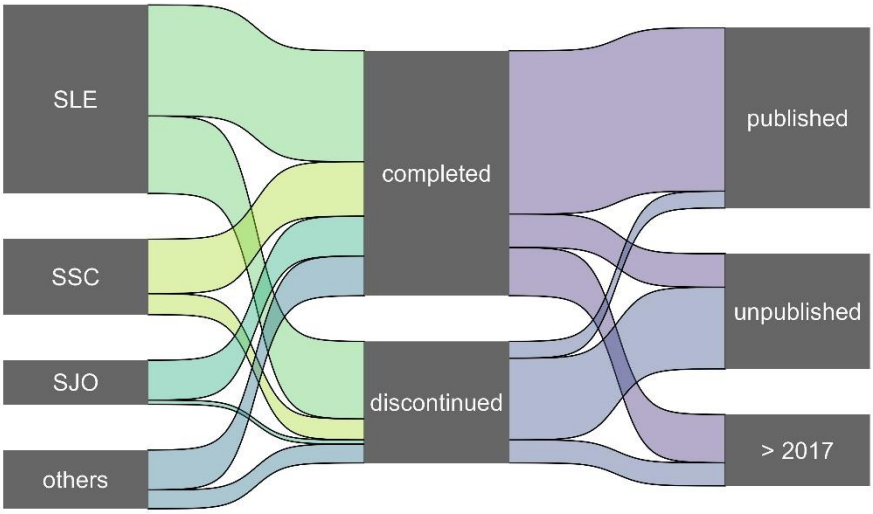


Figure 2. Completion and publication status of studies according to the disease investigated.



SLE. systemic lupus erythematosus; **SSC.** systemic sclerosis; **SJO.** Sjögren syndrome; **>2017** refers to those studies completed after 1st Janvier 2017 for which their publication status has not been checked.

Figure 3. Included studies and their planned sample size (vertical axis) grouped according to the disease, their publication status, and their completion status .