Are Metastatic Breast Cancer Clinical Trials in Germany Reporting Results in Accordance with the WHO Joint Statement? – Protocol for a Mixed Methods Study

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Background

The Declaration of Helsinki states that all interventional clinical trials must make their results publicly available. The 2017 World Health Organisation "Joint statement on public disclosure of results from clinical trials" (WHO Joint Statement)[1] states that clinical trial results should be made public on trial registries within 12 months of trial completion. A May 2022 World Health Assembly resolution on clinical trials[2] reaffirmed the salience of the WHO Joint Statement.

In addition, the European Union Clinical Trial Regulation requires the results of some trials to be made public on the European registries within 12 months of trial completion.[3] U.S. legislation, which also applies to some trials in Europe, also mandates a 12-month disclosure timeframe.[4]

Recent research has shown that German clinical trial sponsors do not consistently adhere to Helsinki ethical imperatives and WHO best practices, and do not consistently comply with European and American disclosure requirements.

Delays in making clinical trial results public can slow down the development and adoption of new, improved treatments. Non-publication of trial results leaves gaps in the medical evidence base.

Objectives

The primary objective of this study is to assess how many clinical trials in the cohort have never made their results public in the academic literature, and the number of participants in these trials.

The secondary objective of this study is to assess the time to publication for the trials in the cohort that have made their results public in the academic literature, and the number of participants in these trials.

Hypothesis

The study hypothesis is that the results of some clinical trials in the cohort are not made public at all, and that the results of the remaining trials are sometimes only made public in the academic literature more than 12 months post primary completion date.

[1] WHO Joint Statement on Public Disclosure of Results from Clinical Trials: https://www.who.int/news/item/18-05-2017-joint-statement-on-registration
[2] WHO seventy-fifth World Health Assembly – Daily Update: 25th May 2022: https://www.who.int/news/item/25-05-2022-seventy-fifth-world-health-assembly---daily-update--25-may-2022
[3] European Medicines Agency Clinical Trials Regulation: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation
[4] FDA Clinical Trial Guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents

Methodology

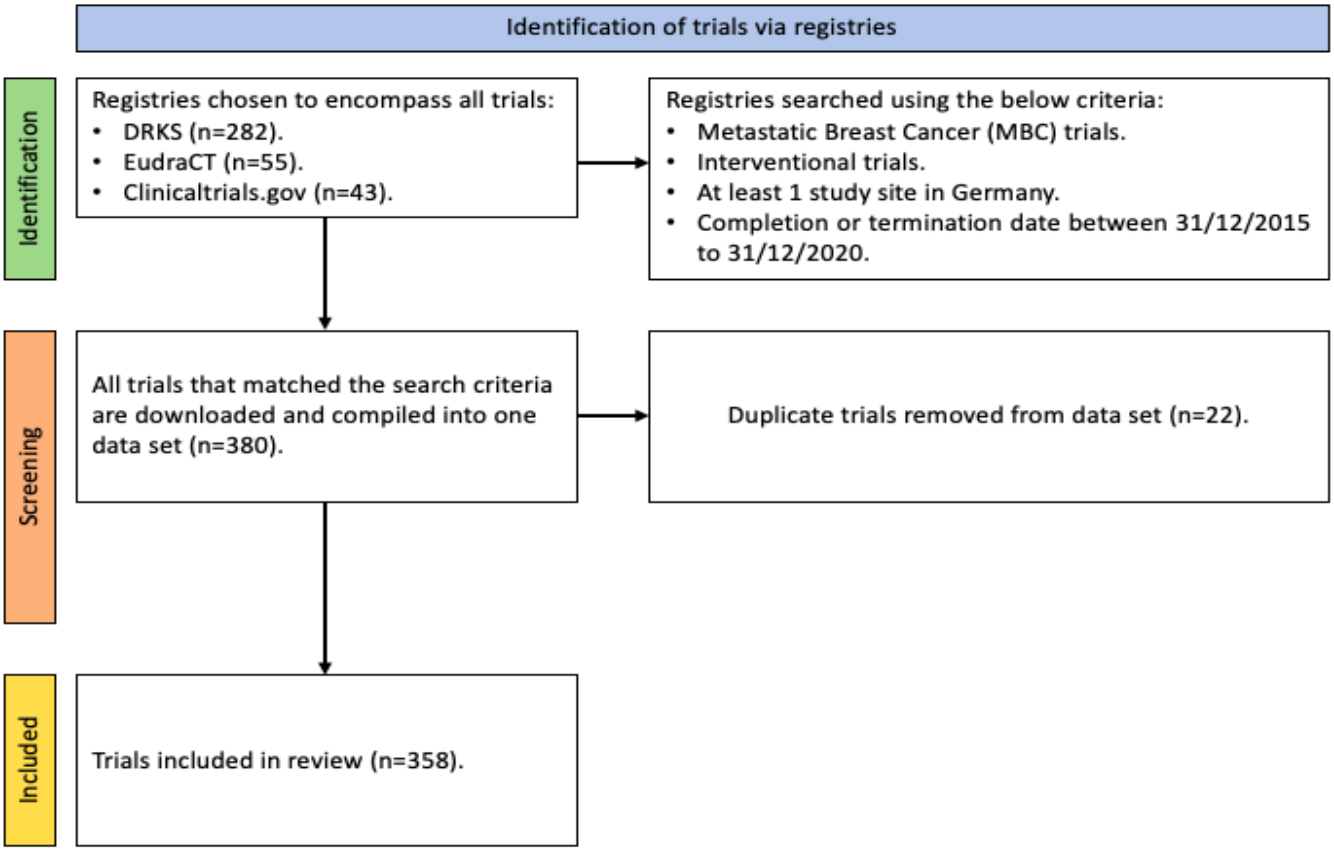
1. Cohort selection

A team member (DG) searched trial registries for MBC trials using the following criteria:

- "Metastatic Breast Cancer" as the condition/disease, in the trial title, and in 'other terms'
- Interventional trials (including non-drug and behavioural)
- At least 1 study site in Germany
- Completion or termination date between 01/01/2016 to 31/12/2020

We applied these search criteria to three public registry databases: ClinicalTrials.gov, EudraCT, and DRKS. We then downloaded all available trials that matched these criteria, removed duplicates, and carried out manual checks for missing values.

Chart 1: Process of acquiring the clinical trial data set representative of the study requirements



Duplicate trials were removed manually by searching for other trial identification numbers and IDs. If a trial was listed on multiple registries, the trial included in the data set was chosen in the following order: CT.gov, EudraCT, DRKS. This is based on the ease of acquiring information from the trial registry websites (e.g., CT.gov provides the best source of downloading mass data). Throughout the process of manual checks for missing data and trial results, all available websites where the trial is listed will be used (e.g., if the trial is listed on both CT.gov and DRKS, both websites will be checked for missing information and results availability).

Table 1: Total number of trials included in the final review, per registry

	Registry	Acronym	No. of Clinical Trials that match the Search Criteria (duplicates excluded)
1	Deutsches Register Klinischer Studien	DRKS	282
2	European Union Drug Regulating Authorities Clinical Trials Database	EudraCT	33
3	U.S. Federal Government database of clinical trials	CT.gov	43
			Total = 358

Thus, the final cohort consists of 358 interventional clinical trials involving potential treatments for metastatic breast cancer conducted during 2016-2020 that involved at least one study site in Germany.

The Declaration of Helsinki and the WHO Joint Statement are both applicable to all trials in the study cohort. Trials were included regardless of whether or not they were and/or are subject to legal or regulatory reporting requirements in any jurisdiction.

2. First literature search

For each of the included trials, a team member will search for results using a 4-step process:

1) Scanning of the "results" section of the relevant trial registry for tabular summary results [note: DRKS does not have a tabular summary results section].
2) Scanning of the "results" section of the relevant trial registry for publications that have either been uploaded by sponsor/investigator or automatically indexed by the registry.
3) The clinical trial identifier (NCT, DRKS, EUCTR number) will be entered on Google Scholar. The first 2 pages will be searched for potential matches.
4) Google Scholar will be searched by entering the following search terms: title and principal investigator name. In the search, the name will be put into "quotation marks", but not the title. The first 2 pages will be searched for potential matches.

For all steps, if a publication is found it will be verified that it is indeed a results publication for the study and not only a mention of the registry ID in a different context (for example a review of multiple trials, or a trial protocol). This verification is performed based on title and abstract of the publication and if needed by referring to the full text. In case we identify publications, the hyperlink to the publication and the publication date[5] will be extracted.

If the publication is not a final results publication reporting on a trial's primary outcome measure, the publication search will be continued. If a results publication is found, we stop the publication search for this trial at that step. If no hit occurs, we will proceed to the next step.

In line with common practice in this field, we will only classify articles published in peer-reviewed journals and PhD theses as publications. We will not count conference abstracts, posters, presentation slides, or other grey literature as publications, but will capture those separately in the spreadsheet as 'grey literature'.

Only if all four searches stay without results, the study will be characterized as "no publication found".

> *Note: If any trial's putative outcome publication date precedes its primary completion date, we will review the publication and assess whether it qualifies a full outcome publication.*

3. Validation of findings

All outreach to trial sponsors will identify the study as being run by TranspariMED. All emails will disclose that TranspariMED plans to proactively share the results of this study with the media. In case of non-response, one reminder email will be sent. The team will not reach out to principal investigators as the ultimate responsibility for safeguarding adherence to ethical imperatives and WHO best practices lies with the company or institution that sponsored a trial.

The team will reach out by email to the press offices (or where not available, other public contact emails stated on sponsors' websites) of sponsors of those trials for which no results could be located, and invite sponsors to (a) flag any relevant publications that the study team may have overlooked, and to (b) provide a short on-the-record statement on their clinical trial reporting policies and plans for inclusion in a supplementary annex of the final manuscript.

[5] For studies providing only month/year, the first day of the month is used. The earliest date the article was published in any format will be recorded.

4. Second literature search

As an additional quality control measure, we will run a second search for publications for those clinical trials where the first search did not return publications, and where the sponsor did not provide information on the publication status of the trial.

We will search for results using a 4-step process:

1) The "results" section of the relevant trial registry will be scanned for (a) tabular summary results and (b) other publications [repeat of the earlier search in case results have been submitted or published in the meantime]
2) PubMed will be searched for the clinical trial identifier (NCT, DRKS, EUCTR number)
3) PubMed will be searched for +"intervention name" and +"condition name" (both in "quotation marks" and preceded by a + sign). The first 2 pages will be searched for potential matches.
4) Google Scholar will be searched for +"intervention name" and +"condition name" (both in "quotation marks" and preceded by a + sign). The first 2 pages will be searched for potential matches.

Outcome Measures

The primary outcome measures are (a) the extent and (b) the speed of trial outcomes publication in a peer-reviewed journal or PhD thesis for trials missing tabular summary results on the registry.

We will calculate time to publication by calculating the time difference between a trial's primary completion date and the date the trial's outcomes were first made public in a peer-reviewed journal.

We anticipate including a narrative discussion of several trials in our manuscript to highlight the scientific, clinical and/or fiduciary implications of late and/or non-reporting of clinical trial results.

Summary Statistics

Table 1: Publication speed and research waste in MBC clinical trials, % of trials

	Timely publication	Delayed publication			Research waste	Publication speed (months, average)*
	Within 1 year	Within 1-2 years	Within 2-3 years	After 3 years	No results	
All trials	5%	11%	24%	27%	33%	27.4

** Calculated for reported trials only [Note: outcome numbers above are purely illustrative.]*

Table 2: Publication speed and research waste in MBC clinical trials, # of patients

	Patients total	Timely publication	Delayed publication			Research waste
		Within 1 year	Within 1-2 years	Within 2-3 years	After 3 years	No results
All trials	10,035	450	1,343	Etc		

Table 3: Publication speed and research waste in MBC clinical trials, # of trials

	Trials total	Timely publication	Delayed publication			Research waste
		Within 1 year	Within 1-2 years	Within 2-3 years	After 3 years	No results
All trials	488	23	Etc			

[PROTOCOL ENDS]