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# Reporting of Older Subgroups in FDA/EMA Registration Trial for DLBCL, 2017-2023

Forked from Reporting of Older Subgroups in FDA/EMA Registration Trial for DLBCL, 2018-2023

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**Protocol status:** Working
**This protocol is an update that includes just one year of approval inclusion in addition**

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## Abstract

Reporting of Older Subgroups in FDA/EMA Registration Trial for DLBCL, 2017-2023

## Anticipated or actual start date

1 2024/10/25

## Language

2 English

## Reporting of Older Subgroups in FDA/EMA Registration Trial for DLBCL, 2017-2023

3 Reporting of Older Subgroups in FDA/EMA Registration Trial for DLBCL, 2017-2023

## Anticipated completion date

4 2025/06/12

## Stage of review at time of this submission

5 Review process started

## Named contact

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## Review team members and their organisational affiliations

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## Funding sources/sponsors

8 No funding sought.

## Conflicts of interest

9 Pallawi Torka reports a relationship with Genmab US Inc that includes: consulting or advisory. Pallawi
Torka reports a relationship with Genentech USA Inc South San Francisco that includes: consulting or
advisory. Pallawi Torka reports a relationship with Seagen Inc that includes: consulting or advisory.
Pallawi Torka reports a relationship with Seagen Inc that includes: consulting or advisory. Pallawi
Torka reports a relationship with AbbVie Inc that includes: consulting or advisory. Pallawi Torka
reports a relationship with Bristol-Myers Squibb Company that includes: consulting or advisory.
Pallawi Torka reports a relationship with Lilly Oncology that includes: consulting or advisory. Nina
Rosa Neuendorff reports a relationship with Janssen-Cilag SAS that includes: travel reimbursement.
Nina Rosa Neuendorff reports a relationship with Medac that includes: travel reimbursement. Nina
Rosa Neuendorff reports a relationship with Novartis that includes: travel reimbursement. Nina Rosa
Neuendorff reports a relationship with Pfizer Inc that includes: travel reimbursement. Nina Rosa
Neuendorff reports a relationship with AbbVie Inc that includes: travel reimbursement. Nina Rosa
Neuendorff reports a relationship with Jazz Pharmaceuticals Inc that includes: travel reimbursement.
If there are other authors, they declare that they have no known competing financial interests or
personal relationships that could have appeared to influence the work reported in this paper.

## 14. Collaborators

10 Colm Mac Eochagáin, Oncologist, Dublin

## Review question

11 Population:
Older patients enrolled to FDA and EMA registration clinical trials of chemo-, immune- and targeted therapies for diffuse large B-cell lymphoma (DLBCL), where FDA and/or EMA registration was granted between 2017-2023. Intervention: Studies assessing chemo-, immune- and targeted therapies for DLBCL, and leading to FDA and/or registration between 2017-2023 will be included. Trials defined as paediatric trials or trials with a mean participant age of under 18 years will be excluded. Registration trials assessing such therapies in other lymphoma entities will also be excluded. Approvals relating exclusively to biosimilar or alternative formulation indications will be also excluded. Comparator: Studies including any comparator; including no comparator, or placebo comparators, will be included. Outcome: Reporting completeness for older subgroups enrolled to FDA and/or EMA registration studies of chemo-, immune- and targeted therapies for DLBCL, where such registration was granted between 2017-2023. The following domains will be systematically and hierarchically assessed according to criteria established by Chan & Altman (10.1001/jama.291.20.2457), and developed by MacEochagain & Battisti (10.1007/s10549-023-07081-0):

- (Protocol-defined) Clinical Efficacy Endpoints among the older subgroup
- Baseline characteristics among the older subgroup
- Health-related quality of life among the older subgroup
- Toxicity among the older subgroup

The following domains will be assessed using descriptive statistics, as appropriate:

- % of patients within the older subgroup
- % of total enrolment stratified by ECOG score
- Conduct and reporting of Baseline Geriatric Assessment
- Conduct and reporting of Geriatric-Specific Geriatric PRO Outcome Metrics
- Textual analysis of trial inclusion and exclusion criteria, including renal impairment and cardiac
comorbidities
- Textual analysis of efficacy outcomes
- Trial characteristics (including but not limited to: trial phase, enrolment size, treatment setting)

## Searches

12 MEDLINE/PubMed/CINAHL/EMBASE/Web of Science are searched on 28/10/2024 and 2025/05/15 in accordance with the search strategy outlined in the respective section. The search strategy was devised in collaboration with Celine Soudant, librarian at MSKCC Library. Publications between 01/01/2000 and 2025/05/15 will be included. Pre-prints and conference abstracts will be considered as some of the registration trials were finished recently.

## URL to search strategy

13 To be added after completion of review.

## Condition or domain being studied

14 Reporting of older subgroups enrolled to FDA and/or EMA registration trials of chemo-, immuno- and targeted therapies for DLBCL (2017-2023).

## Participants/population

15 Subgroup reporting of 'older subgroups' enrolled to registration trials (2017-2023) in chemo-, immune- and targeted therapies for DLBCL will be assessed. In accordance with established precedent within
medical literature, 'older subgroups' will generally be defined as subgroups of patients aged 65 and older. An absolute minimum of 60 years will be used to define an 'older subgroup' where a stratification threshold of 65 years is not provided by individual studies.

## Intervention(s), exposure(s)

16 All studies leading to Food and Drug Administration and/or European Medical Agency registration
of chemo-, immuno- and targeted therapies indicated for DLBCL in the adult populations, where registration was granted between 2017-2023 inclusive, will be included, with exclusion criteria as previously described herein. Chemotherapy includes cytostatic drugs, immunotherapy includes cellular therapies as well as monoclonal and bispecific antibodies, targeted therapies include immunomodulatory drugs and tyrosine-kinase-inhibitor, whether given as monotherapy, or combination therapy, regardless of whether this treatment was given in the curative or palliative setting.

## Comparator(s)/control

17 Studies including any comparator; including no comparator, or placebo comparators, and multi-arm studies, will be included.

## Types of study to be included

18 Inclusion Criteria: All studies leading to Food and Drug Administration and/or European Medical Agency of chemo-, immune- and targeted therapy indications in DLBCL, where registration was granted between 2017-2023 inclusive, will be included. Identified trials will be assessed for the presence of both primary and secondary peer-reviewed publications containing or potentially containing information regarding older subgroups enrolled to the study, as outlined in the search strategy. Data and publication references archived at the trial's clinicaltrials.org repository will also be assessed for older-population subgroup data. Review and compilation of data sources will be carried out by two reviewers working independently. Scoring of individual trials will be conducted by two (different) reviewers, working independently, with conflicts resolved by consensus.
Exclusion Criteria:
- Review papers
- Preclinical focus
- Wrong Study
- Economic Analyses
- Publications not in English, or without an English translation
- Meta-analyses / combined analyses
- Real world data
- Commentaries
- Guidelines
- Errata
- Data not in the public domain
- Pharmacokinetic studies

## Context

19 Individual PubMed/MEDLINE/EMBASE/CINAHL/Web of Science searches will be conducted for each included clinical trial, as outlined in the search strategy. Search results will be screened using Covidence
(Title/Abstract) by two reviewers for relevant, or potentially relevant primary or secondary publications, which may contain information relating to older subgroups enrolled to the study. Relevant data sources relating to individual trials will be compiled in datasets according to the underlying clinical trial. Each trial-level dataset will comprise all of the available published data for that individual study (i.e. relevant or potentially relevant publications, including such publications' supplementary information, as well as results

reported in the trial's ClinicalTrials.gov repository). Review, extraction, and compilation of geriatric subgroup information for individual trials from individual trial datasets will be carried out by two reviewers working independently, using the Covidence tool for systematic reviews. Scoring of individual trials will be conducted by two (different) reviewers, working independently, with conflicts resolved by consensus.

## Main outcome(s)

20 Efficacy endpoints will be determined with reference to the most recent available study protocol or statistical analysis plan. In instances where no protocol or statistical analysis plan is available in the public domain, reference will be made to licensing authority documentation. Where studies assess efficacy across multiple timepoints, or according to multiple definitions, (for instance: Overall Survival (OS) assessed at year 1, 2, 3, or Progression-Free Survival (PFS) assessed both centrally and by local investigators), these will be considered as a single endpoint; provided data is available for at least one of
the defined components within such compound endpoints, these data will be considered to be assessable. Where endpoints are defined hierarchically and differentially in the protocol as distinct primary and secondary endpoints (i.e. primary endpoint: PFS in the intention to treat population; secondary endpoint: PFS in the population with brain metastases), these will be considered to be separate endpoints.
Measures of effect:
Reporting completeness for efficacy endpoints will be assessed and categorized as being either complete, partial, qualitative, or unreported, according to hierarchical criteria assessing the availability of data relating to sample size, effect size, and measures of precision, as well as requirements to satisfy criteria
for inclusion in meta-analysis, which vary according to the statistical characteristics of the data examined (i.e. paired or unpaired, continuous or binary, or survival data as follows:
- Level of Reporting: Complete; Reported Data:
o Number of participants per group, Effect size, Precision or precise P value for continuous data
o Sufficient for Inclusion in Metaanalysis: Yes
- Level of Reporting: Partial; Reported Data:
o Effect size or precision (± p value ± sample size)
o Sufficient for Inclusion in Metaanalysis: No
- Level of Reporting: Qualitative; Reported Data:
o P value ± sample size
o Sufficient for Inclusion in Metaanalysis: No
- Level of Reporting: Unreported; Reported Data:
o Not available
Sufficient for Inclusion in Metaanalysis: No

## Additional outcome(s)

21 - Baseline characteristics
- Health related Quality of Life
- Toxicity
- Trial characteristics including:
o % of patients within the older subgroup
o % of total enrolment stratified by ECOG score
o Conduct and reporting of Baseline Geriatric Assessment
o Conduct and reporting of Geriatric-Specific Geriatric PRO Outcome Metrics
o Textual analysis of trial inclusion and exclusion criteria including organ impairments
o Textual analysis of efficacy outcomes
o Other trial characteristics (including but not limited to: trial phase, enrolment size, treatment setting)

Measures of effect:
Scoring of Baseline characteristic, Health related Quality of Life, and Toxicity Domains:
Domain Minimum Threshold:
Baseline characteristics
- Performance status OR comorbidities AND
- ≥1 Key prognostic OR predictive factor(s)

Toxicity
≥3 Key toxicity Domain(s) by organ site
OR
Overall G3 toxicity AND 1 key toxicity domain

HRQOL
≥1 Validated HRQOL instrument(s)

Level of reporting Reported Data
Complete: Meets minimum threshold; including numerical data sufficient for inclusion in meta-analysis
Partial: Meets minimum threshold; including numerical data insufficient for inclusion in meta-analysis
Qualitative: Meets minimum threshold; without numerical data
Unreported: Does not meet minimum threshold

Reporting of other domains, as described before, will be by descriptive statistical methods

## Data extraction (selection and coding)

22 Food and Drug Administration and European Medicines Agency oncology approvals for DLBCL granted
between 01/01/2017 and 31/12/2023 will be retrieved from publicly available FDA sources (Center for Drug Evaluation, Research. Drug Approvals and Databases. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases) and from publicly available EMA resources (European Medicines Agency, https://www.ema.europa.eu). Studies relating to approval of biosimilar, alternative formulation, paediatric (as defined by the study authors, or where mean/median participant age is 18), and other lymphoma entity indications, will be excluded. Individual PubMed/MEDLINE/EMBASE/CINAHL/Web of Science searches will be conducted for each included clinical trial, as outlined in the search strategy. Search results will be screened using Covidence (Title/Abstract) by two reviewers for relevant, or potentially relevant primary or secondary publications, which may contain information relating to older subgroups enrolled to the study. Included studies will be assessed in full, including publication supplements and data archived at the study's ClinicalTrials.gov repository, by two reviewers.
Data relating to the following domains (as they relate to older subgroups) will be collected:
- Clinical Efficacy Endpoints (as defined by the study protocol / statistical analysis plan)
- Baseline characteristics
- Health-related quality of life
- Toxicity
- % of patients within the older subgroup
- % of total enrolment stratified by ECOG score
- Conduct and reporting of Baseline Geriatric Assessment Conduct and reporting of Geriatric-Specific
Geriatric PRO Outcome Metrics
- Textual analysis of trial inclusion and exclusion criteria (including organ impairments).
Following screening and compiling of data from relevant publications, the completeness of reporting for individual trials will be scored by all reviewers according to hierarchical criteria established by Chan & Altman (10.1001/jama.291.20.2457), and further developed by MacEochagain & Battisti (10.1007/s10549-023-07081-0).

## Risk of bias (quality) assessment

23 Risk of bias will not be formally assessed. This study will assess outcome reporting, rather than treatment effect.

## Strategy for data synthesis

24 This study aims to assess the completeness and adequacy of reporting among older subgroups, without intending to undertake cross-trial comparisons, meta-analysis, or synthesis of data across or between trials. All data results presented will be descriptive in nature. No meta-analysis of collected data is planned.

## Analysis of subgroups or subsets

25 Not applicable. The intention of the review is to assess older subgroups, as previously defined. Analysis of
subgroups (i.e. according to gender, ECOG, clinical stage, etc) within this (older) population are not planned.

## Type and method of review

26 Systematic review

## Health area of the review

27 hematology, geriatric hematology

## Language

28 English

## Country

29 Germany, USA

## Other Registration Details

30 Not applicable

## Dissemination Plans

31 This review will be published in an international peer reviewed journal focussing on cancer, hematology, or geriatric oncology.

## Keywords

32 Systematic
review; geriatric hematology, subgroup, reporting, bias, cancer, diffuse large B-cell lymphoma; CAR-T cell therapy; bispecific antibody; monoclonal antibody

## Current review status

33 Review process started