Statistical analysis and reporting of adverse events in clinical trials: recommendations, current practice and relevance for interpretation

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Summary

Clinical trials are used to empirically verify the efficacy and safety of new medical treatment methods. Benefits and harms are evaluated to perform a benefit-risk assessment of a new treatment method. Since the focus in the presentation on phase 3 clinical trial results is usually on the benefits, the harms might not be presented in sufficient detail. For this paper, the focus was therefore placed on how adverse events should be and are reported in publications on phase 3 clinical trials.

At the beginning, existing recommendations for the presentation of adverse events in publications are identified. The focus is on the CONSORT statement with its extensions, as well as the guidelines of the journals The Lancet and New England Journal of Medicine. A catalogue of quality criteria for AE reporting is then compiled from these suggestions. This catalogue is then used to examine various recent publications to see how well they already represent adverse events. Subsequently, with the help of data from the TRIANGLE trial, an attempt is made to create the best possible harms representation. In doing so, the differences between the different codings of adverse events, MedDRA and CTCAE, are also considered.

In the catalogue of criteria, a total of 17 criteria can be found that an article can fulfil. In total 50 articles were found by searching the journals New England Journal of Medicine and The Lancet for publications on phase 3 clinical trials. This was done using the term phase 3. Since the full texts of the papers from the different journals are only available in different time periods via the university library, the study periods for the two journals differ. For the New England Journal of Medicine the time period was from 01.01.2023 to 28.02.2023. For The Lancet the time period was from 01.09.2019 to 31.12.2019. In total 33 articles were analysed because all other articles were not phase 3 clinical trials. It was found that on average just 7.18 [0;10.5] of the 17 criteria are fulfilled by an article. This is clearly less than half of the criteria. The best article fulfilled only 10.5 criteria, while one article did not even fulfil a single criterion. Differences were also seen between the journals examined. While articles from the New England Journal of Medicine met an average of 6.36 [0;10] criteria, articles from The Lancet met an average of 7.79 [5.5;10.5] criteria. There was no difference between papers from oncology, with an average of 7.08 [0;10.5] criteria fulfilled, and other medical fields, with an average of 7.32 [4;10] criteria fulfilled. Criteria 1), says whether title or abstract states that AEs are

addressed - fulfilled 25 times, 15), states whether no generic or vague descriptions of harms is used - fulfilled 25 times, and 16), states whether harms and benefits are addressed equally in discussion - fulfilled 30 times - were met most frequently. In contrast the criteria 3 ii), states whether used cut-offs were explained - not fulfilled once, 7), says whether recurrent events in same patient are counted as separate events or not - fulfilled once, and 14 ii), states whether AEs of different severity grades were not combined in reporting - not fulfilled in any case - were met least frequently.

Subsequently, an attempt was made to create a presentation with the help of the TRIANGLE trial data that fulfilled all criteria as far as possible. This was achieved, but only in a very long form, and thus not everything would fit into a publication. This shows that it is not easy to fulfil all the criteria mentioned in the main body of a publication, but there is the possibility of doing so in the supplementary material. Furthermore, a comparison was made between the reported adverse event preferred terms, according to MedDRA definition, and the manually reclassified adverse event preferred terms, according to CTCAE V.4.03 definition. Clear differences can only be seen for very few PTs, but these are the important ones. Furthermore, a comparison was made between the reported and reclassified terms, in which some differences were seen that suggest a possible underreporting of harms by the MedDRA coding in the reported terms. This is particularly noticeable in the PTs of the SOC category Infections and infestations. Another point that stood out is the large increase in AEs in SOC term Blood and lymphatic system disorders, which is accompanied by a clear decrease in AEs in SOC term Investigations. However, in order to be able to make generally valid statements about underreporting, a more comprehensive analysis would have to be carried out in which all PTs are then thoroughly reclassified.

In conclusion, it can be said that there are already some proposals on how adverse events should be presented. However, consideration needs to improve further. Therefore, in the future there should be a binding checklist for the presentation of adverse events that must be adhered to in order for a paper to be published. This checklist should then function as an extension of the CONSORT statements, which should already be taken into account during the preparation of the study and not only during publication. This is also advantageous in that new treatment methods can then be better compared on the basis of scientific publications and additional information is not required.

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Abbreviations

Abbreviation	Definition
AE	**a**dverse **e**vent
ASCT	**a**utologous **s**tem **c**ell **t**ransplantation
AT	**A**s **T**reated
CI	**c**onfidence **i**nterval
CONSORT	**CON**solidated **S**tandards **O**f **R**eporting **T**rials
CTCAE	**C**ommon **T**erminology **C**riteria for **A**dverse **E**vent
eCRF	**e**lectronic **c**ase **r**eport **f**orm
EMA	**E**uropean **M**edicines **A**gency
FDA	US **F**ood and **D**rug **A**dministration
ICH	The **I**nternational **C**ouncil for **H**armonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	**I**nternational **C**ommittee of **M**edical **J**ournal **E**ditors
ITT	**I**ntention **t**o **t**reat analysis set
MCL	**M**antle **c**ell **l**ymphoma
MedDRA	**Med**ical **D**ictionary for **R**egulatory **A**ctivities
NEJM	**N**ew **E**ngland **J**ournal of **M**edicine
PP	**P**er **P**rotocol set
PT	**P**referred **T**erm
QoL	**Q**uality **o**f **L**ife
RCT	**R**andomised **C**ontrolled **T**rial
SAE	**s**erious **a**dverse **e**vent
SOC	**S**ystem **O**rgan **C**lass
TRIANGLE trial	Autologous **T**ransplantation after a **R**ituximab/**I**brutinib/**A**ra-C containing i**n**-duction in **g**eneralized mantle cell **L**ymphoma - a randomized **E**uropean MCL Network **trial**

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1 Introduction

Clinical trials are used to empirically verify the efficacy and safety of new medical treatment methods. Statistical evaluation plays an important role in presenting the results of clinical trials in a relevant and comprehensible way. While efficacy is often the primary concern of clinical trials in later phases, the evaluation of safety is the primary concern in early phases. Both are necessary to perform a benefit-risk assessment of a new treatment method. Based on this evaluation, the responsible authorities, in Europe the European Medicines Agency (EMA) and in America the US Food and Drug Administration (FDA), then decide whether to approve the new drug.

The evaluation of safety is normally done by a collection of adverse events (AEs) which can have a major impact on whether a particular intervention will be deemed acceptable and useful. An AE is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment”, which is given on page two of the The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A guideline.[49] The AE collection in clinical trials is highly regulated by authorities in order to respond promptly to unexpected side effects of novel therapies. Although these are already considered in earlier phases, the recording of AEs also plays a role in later phases. Rare AEs in particular cannot be observed in earlier phases due to the small number of study participants. Although they are recorded in every study, there is still no fixed procedure in the statistical analysis of AEs. Various problems arise, such as different classifications of AEs, resulting in clearly different frequencies. The question of how to deal with multiple AEs in one patient may also cause difficulties.

This bachelor thesis will examine how AEs in phase 3 clinical trials are statistically evaluated and how the results are shown in publications in regard to the problems that could arise. In publications on phase 3 clinical trials, the presentation of the efficacy of the new treatment is usually strongly prioritised, while the presentation of AEs usually plays a secondary role, although the reporting of AEs is amongst the most important elements of a clinical trial publication. Firstly, recommendations for statistical evaluation from regulatory agencies and from other scientific studies are reviewed. Based on these, various phase 3 trial publications are examined, focusing on the extent to which the re-

commendations are implemented. Furthermore, a statistical analysis will be performed using data from the “Autologous Transplantation after a Rituximab/Ibrutinib/Ara-C containing induction in generalized mantle cell Lymphoma - a randomized European MCL Network trial” (TRIANGLE trial).[1] With this data it is tried to get a nearly perfect harms analysis, like it could be done in a publication. Furthermore, the occurring differences between the different definitions for the used AE terms are examined.

2 How adverse events should be reported in phase 3 clinical trial publications

2.1 Safety recommendations as an extension of the CONSORT statement

Firstly, it will be examined how AEs should be presented in publications of phase 3 clinical trials. There are no regulatory requirements for the presentation of AEs in publications, but there are recommendations from various quarters. Probably the best-known are from the Consolidated Standards Of Reporting Trials (CONSORT) group and will now be examined in more detail.[50] The ICH efficacy guidelines were not investigated because the focus will be on the representation of AEs in publications.

The CONSORT group has drawn up a checklist for publications of phase 3 randomised controlled trials (RCTs), which comprises a total of 22 items. The items refer to all parts of a publication, from the title of the publication to the methods of analysis used and the results found. Item 19 on said checklist is concerned with AEs and therefore bears the most relevance for this thesis. It states that "all important AEs or side effects of each intervention group"[50] should be presented in the publication.

This very general statement by the CONSORT group was expanded in the paper "Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT statement"[2], with ten suggestions given specifically for reporting harms in publications.

The first two recommendations relate to title and abstract of the publication as well as its introduction. They say that if data have been collected for both benefits and harms, the abstract and introduction should state this. The title should reveal whether the harms analysis was a primary study objective.

Next, it is suggested that all AEs should be listed with known definitions, for example according to the Medical Dictionary of Regulatory Activities (MedDRA) or the Common Terminology Criteria for Adverse Events (CTCAE), in the publication. If new definitions are used, they should be explicit and clearly formulated and presented. In addition, if standardised and validated measurement instruments were used, a description of them needs to be provided. It should also be made clear whether all AEs were reported or only selected parts. If only a selected sample is reported, for example if filtering was

done by graduation or relevance of AEs, expectation or cut-offs, it should be clearly explained who made the filtering decisions and why. Furthermore, a distinction between expected and unexpected AEs is to be made because results can be different for those two situations.

The fourth recommendation states that it is advisable to clarify how harm-related information has been collected. In particular, the following points need clarification: Firstly, the mode of data collection as well as different attribution methods need clarification, since different control methods can lead to a higher number of AEs occurring. Also an other classification of reported AEs, for example the difference between MedDRA and CTCAE classification, can lead to different results. Furthermore, the time interval in which AEs are reported must be precisely defined. The starting point is usually clear and begins with the administration of the first dose of medication, but the endpoint is necessary to be defined, as side effects sometimes first occur weeks or months after taking medication. Therefore, a follow-up phase is normally part of a study, in which AEs that occur later can be observed. For example, 60 days after a patient's treatment discontinuation could be chosen as follow-up time period, but it depends, for instance, on the medication administered or the expected latency and duration of side effects. Again, for all decisions it should be made clear in the publication who made them and why. Particular attention is necessary for AEs that have led to treatment discontinuation or withdrawals from the study. These AEs usually have a serious impact on the patient's quality of life (QoL), which is why they should occur as rarely as possible. If they occur very frequently and therefore many patients withdraw from the study, one should think about different strategies to avoid them. Some possibilities would be to reduce the dose of the medication or to pause the therapy for a certain period of time. A last resort is to discontinue the study entirely. Therefore, for every RCT a plan on how harms are monitored and when and why the study needs to be stopped due to harms is essential. If possible, this plan should also be briefly outlined in the publication, even if it has not been implemented.

Furthermore, the statistical methods used should be briefly described in the publication. This can be done by describing a plan on how the harms will be analysed and presented in the publication. In doing so, one should include AE coding, describe the handling of recurrent events, specify timing issues, describe handling of continuous measures and any other statistical analysis that has been done.

For subgroups formed for the analysis, for example a division according to age groups, it is necessary to indicate whether they were formed post hoc or a priori. Descriptive analyses are usually used for the presentation of AEs in publications due to the lack of power in the studies, which makes inferential statistical analyses like statistical tests difficult to interpret. In addition, incidence rates, period prevalence rates and point prevalence rates can provide complementary information on the occurrence of AEs. Kaplan-Meier curves can be useful for plotting AEs, especially when survival is a primary endpoint. For continuous variables, the mean, standard deviation, median and interquartile range should be reported. In the case of inferential statistics for harm outcomes, for example to perform statistical tests to see if there are significantly fewer AEs in a treatment group, one should be aware of the following problems. On the one hand, there is the problem of low power for uncommon events. On the other hand, one may need adjustment for multiple testing problems. Also, one could have composite outcomes, regression to the mean and heterogeneity of treatment effects across prespecified subgroups.

As described above, AEs that lead to premature discontinuation or withdrawal from the study by the patient should be described in more detail in the publication. For each treatment arm the withdrawals due to harms as well as the experience with the administered treatment ought to be described. A separate description of early and late withdrawals is advisable. Deaths have to be mentioned, even if they are not related to the medication administered. In addition, it is recommended to provide the denominators for analyses on harms which means to state types and definitions for the analyses used. The data set on which the analysis of the harms is carried out should also be specified. In most cases, this is the as treated (AT) analysis set, in which the patients were assigned to the group whose treatment they received.

Moreover, it is suggested that the absolute risk of each AE is presented. In particular, the type should be considered, i.e. whether an AE is study related, possibly treatment related or not study related, or whether it is an expected or unexpected AE. Furthermore, the different grades of occurring AEs must be discussed as well as the seriousness, which indicates whether it is an AE or a serious adverse event (SAE). SAEs are defined by the ICH E2A guideline on page three as follows: “A serious adverse event is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent

or significant disability/incapacity or is a congenital anomaly/birth defect".[49] These must be reported separately to the FDA or its European pendant, the EMA[5], and should therefore also be listed separately in the publication. In addition, appropriate metrics for recurrent events, continuous variables and scale variables are useful to be given. This is possible via graphs as well as tables. Especially for recurrent events or events that occur more than once in a patient, both the number of affected patients and the number of events occurring are supposed to be reported separately.

Also, any subgroup analysis conducted, as well as exploratory analysis for harms, should be cited in the publication. It must be specifically stated how, why and when the subgroup analyses were planned, especially whether a priori or post hoc. Otherwise, the same recommendations apply to subgroup analyses as to the overall analysis which is discussed in this chapter.

Finally, it is said that a balanced discussion of benefits and harms in the publication would be helpful in evaluating the advantages and disadvantages the new treatment has. This is not possible in the methods and results part, in which they are only listed. In addition, one has to consider the focus of the study and should, if possible, pay attention to generalisability. It is highly recommended to report results that contain the following: inconclusive findings, lack of power, multiplicity of comparisons, for post hoc analyses whether it is influenced by data knowledge, as well as short durations of exposure to allocated treatment. Reporting these aspects is vital, even if they are not positive for the study outcome, since they could be more useful for future drug development than significant or clinical relevant results.

In summary, it has been argued that if data on AEs is collected, these events should be listed and defined with reference to standardised criteria like the MedDRA or the CTCAE. For the safety analysis it is recommended to use the term harm analysis instead because harms are the totality of possible adverse consequences of an intervention or therapy. With the information about harms, it is possible to make statements about the safety of a new drug or a new treatment method. Also, the methods used for data collection and attribution of events should be described as well as the absolute risk of each AE occurring in each study arm. In addition, appropriate metrics for recurrent events and the number of participants withdrawn due to harms should be presented.

But the most important point is that the publication needs a balanced discussion of benefits and harms at the end. The approval of new drugs or treatment methods is based on a

benefit-risk assessment. If the benefits of a drug or treatment outweigh the risks of the best existing therapy, the drug or treatment is approved. Therefore, it is sensible to carry out this assessment also in publications and to highlight how the drug works with all its advantages and disadvantages.

2.2 Journals' safety recommendations for publications on their site

Having examined the recommendations of the CONSORT group with an extension for harms in chapter 2.1, this section deals with the journals safety recommendations. As several publications from the journals The Lancet and New England Journal Of Medicine (NEJM) will be examined in Chapter 3 with regard to compliance with the harm recommendations found in these chapters, this chapter will explore the safety recommendations that the journals specify for publications on their pages.

In their requirements for authors, both journals want the recommendations of the International Committee of Medical Journal Editors (ICMJE) to be followed.[9,10] These state that one should follow the instructions of the journals and the reporting guidelines for the respective study types. The RCT guidelines given by the ICMJE are also interesting as they are also dealing with phase 3 RCTs. The ICMJE also provides the recommendations of the CONSORT group for RCTs, which were already considered in chapter 2.1.[11] In addition, the journals have some further requirements for publications. However, in the following, only those that deal with the presentation of harms or AEs will be considered.

While the NEJM does not give any further safety recommendations to authors besides the ICMJE recommendations[10], The Lancet has a few additional ones to authors on how they should present AEs or harms in publications.[8,9]

Firstly, The Lancet emphasises the importance of information on which dataset the safety analysis is performed on. There are three possibilities: the intention to treat (ITT) dataset, the per protocol (PP) dataset and the as treated (AT) dataset. Furthermore, it is assumed that there are summaries of the adverse events, which contain the absolute numbers and percentages for both treatment groups. All treatment-related deaths should be included. Additionally, it is necessary to describe assessment of safety and AEs and all clinically relevant findings. When describing the "estimates of survival - either the median or at a specific time point - they should be accompanied by a 95% confidence interval (CI)"[8]. In addition, "authors must include numbers at risk and are encouraged to include the number of censored patients."[9] If the survival is shown with Kaplan-Meier survival curves, they should "have unbroken y axis, include numbers at risk below x axis and state a measure of effect", such as log-rank p plus hazard ratio and 95% CI.[8]

The guidance shown for Kaplan-Meier curves applies also to other cumulative incidence figures. This guidance is useful for representation of AEs because illustrations, i.e. photographs, graphs or diagrams, are prerequisites for publication in the journal.

2.3 Open questions in safety analyses

Despite the suggestions that have been made by the CONSORT group and the journals, some interesting questions remain unanswered by the given recommendations.

It is often the case that there is a recommendation that a point should appear in the publication, but it is not clear exactly how the point should be treated. For example, it is said that AEs can be presented both as a graph and as a table, but it is not said which form of presentation is to be preferred. Furthermore, it is suggested to present AEs according to the grade to which they occur. However, often only AEs with a certain degree are indicated and reasons should be given why the selection was made. Regardless, there are no recommendations as to which grades should be reported and when. The same applies to frequency cut-offs that are chosen for the representation of AEs. It is also not clear according to which definition the AEs should be presented in the publication, as different definitions according to MedDRA or CTCAE lead to different reporting. Although it is proposed to report the number of AEs that occur additionally and not only the number of patients in whom an AE occurs, what this should look like is not precisely defined. In addition, it is not specified on which of the data sets ITT, AT or PP the evaluation of the AEs should be carried out. For the safety analysis, the AT dataset is usually used, as one is interested in which harms occur with which treatment method, but there is no further recommendation on this point. A final question that remains open is whether and how statistical tests are carried out and included in the publication. The big problem that arises is the power of a test, which is often not very large, and therefore statements based on p values are difficult to reproduce or interpret. Adjustments are also possible due to the multiple testing problem, but there are no clear suggestions for this either. The type of test performed could also play a role.

Evidently, even with the recommendations given for the representation of AEs in RCT publications, it is not clear how to analyse them. Depending on how the questions are answered by the authors and how AEs were evaluated, very different results may appear in the publications. How these differences affect the results is examined in more detail in chapter 4 using data from the TRIANGLE trial.[1]

However, in publications the main focus is usually on benefits, as these are far more conducive to the sale and use of one's own drug than harms. Because of this, and because of the very limited number of pages, tables and figures allowed in a publication, it

is often not possible to include all the important points of the harm analysis presented in the above-mentioned recommendations. If this is the case, it is a feasible option to include the remaining analyses of harms in the supplemental data[3], which is unlimited in length. This way, one has the possibility to present benefits and harms in a balanced way in the actual publication, but at the same time one can offer enough space for the harms analysis, which often gets short shrift but is very important.

Having determined how harms should be presented in publications, a closer look will be taken at how harms are actually reported and how closely the suggestions are adhered to in the following chapter 3.

3 Representation of adverse events in phase 3 clinical trial publications

3.1 Literature research

3.1.1 Used research criteria

Now that different suggestions for the presentation of AEs have been given, in this chapter the implementation in different publications is examined. Therefore, various papers from The Lancet and NEJM have been searched. Access to the full texts of the journals is possible via the university library. The analysis is restricted to pure clinical phase 3 studies and do not consider mixed phase 2/3 studies or split phase 3a or 3b studies. Since the full texts of the papers from the different journals are only available in different time periods via the university library, the study periods for the two journals differ. The aim is to examine a total of about 30 to 40 articles in the end.

In the journal NEJM, full-text access to all newly published papers is available. For this reason, the past two months were taken as investigation period, which means publications from the period from 01.01.2023 to 28.02.2023. Only publications with the exact phrase "phase 3" in the article category research will be looked at, as only the safety evaluations from new phase 3 studies are the focus of this thesis.

From The Lancet, the most recent articles available for full text access are from 2019. In addition to the general journal The Lancet, publications from the The Lancet Oncology are included in the search. As the TRIANGLE trial is used to examine AEs in a study from Oncology in Chapter 4, a closer look at publications from Oncology is taken in this chapter. Again, only publications with the keyword "phase 3" from the article category research have been searched. This keyword was entered in the search field “Find articles with these terms”. For papers from The Lancet, the period from 01.09.2019 to 31.12.2019 will be considered, which means the most recent four months of the journals available paper.

3.1.2 Articles found to be analysed

With the criteria defined in chapter 3.1.1 a total of 19 full text articles were found in the NEJM, of which one article was rejected on basis of the title, as it was a phase 2 study (see Figure 1).

A total of 15 articles were found from the general journal The Lancet. Of these, two articles were rejected because no full text is available, and three more articles because they are not pure phase 3 studies. From The Lancet Oncology, 16 articles were found, seven of which were screened out as they were not phase 3 trial publications. Thus, 19 articles from these two journals are covered (see Table 1).

Overall, a total of 50 articles were selected from the journals, of which 13 articles were eliminated on the basis of title. Thus, a total of 37 articles were found. Based on the full text, another four articles were screened out because they were no phase 3 trial publications. This means that a total of 33 articles will be analysed in the following, as can be seen in Figure 1.

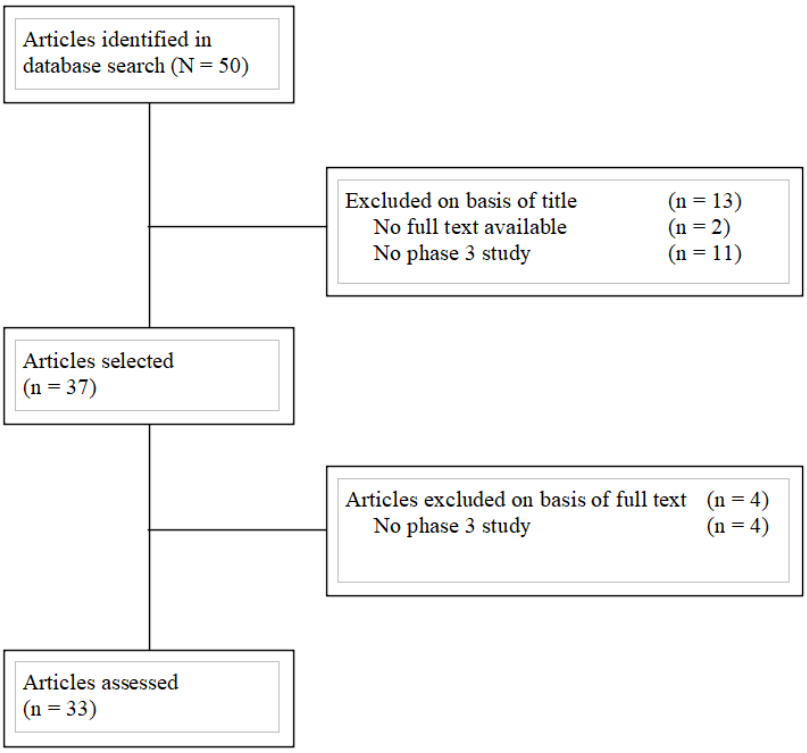

Figure 1: Flowchart of screening of publications included in the analysis

This figure shows how many articles were found in the database search and how many are then also evaluated. It also shows how many articles are excluded and why. It can be seen that of the initial 50 articles, 33 are analysed in the end. Of the 17 excluded articles, 15 were excluded because they are not pure phase 3 studies and two because no full text version is available.

All 37 articles that were not excluded on the basis of title are listed in the references as numbers 12 to 48. The articles excluded on basis of the title are listed as numbers 51 to 63. The NEJM articles are numbered 12 to 29, the Lancet articles are numbered 30 to 39 and the Lancet Oncology articles are numbered 40 to 48. The articles numbered 16, 26, 28 and 29 were excluded based on the full text. As can be seen in Table 1, after the exclusions, 14 articles from the NEJM, ten articles from The Lancet and nine articles from The Lancet Oncology are now analysed. A total of 19 articles can be assigned to the field of oncology, while 14 articles do not come from this field.

Table 1: Characteristics of articles included in analysis (N = 33)

Characteristic	No. of articles [n (%)]
Journal	33 (100%)
NEJM [1]	14 (42%)
Oncology	5 (36%)
Other	9 (64%)
The Lancet	10 (30%)
Oncology	5 (50%)
Other	5 (50%)
The Lancet Oncology	9 (27%)
Other	9 (100%)
Type of medical field	33 (100%)
Oncology	19 (58%)
Other	14 (42%)

[1] NEJM: New England Journal of Medicine

This table shows the characteristics of the articles studied. These are the characteristics by which the articles are divided in the analysis and the differences of which are analysed. In the breakdown by journal, it can be seen that most of the articles come from the New England Journal of Medicine, followed by The Lancet and The Lancet Oncology. In the differentiation by medical field, it can be seen that 19 articles are from oncology and only 14 articles are not from this field.

3.2 Safety criteria to be checked in publications

After the selecting criteria were defined for journal publications in chapter 3.1 and the articles have been found, the criteria will be defined in this chapter on which the harms analysis will be examined. These are made up of the recommendations of the CONSORT group and the journals found and elaborated on in chapter 2.1 and 2.2, as well as the questions that remained open in chapter 2.3. The structure of the recommendations from chapter 2.1 is used, but some points are split up or summarised. A total of 17 points will be examined and evaluated in the analysis of the papers, as can be seen in Table 2.

Table 2: Safety recommendations to be checked in journal publications

Article section	Elements included in paper analysis
Title/Abstract	1) Title or abstract states whether AEs [1] are addressed in study
Introduction	2) Introduction states whether benefits and AEs [1] are addressed in study
Methods	3 i) Article specifies whether reported AEs [1] encompass all the recorded events or just a selected sample 3 ii) If cut-offs/groupings are done, chosen cut-off/grouping criteria are explained. Reasons for different cut-offs used for AEs, SAEs,... explained?
	4) Article specifies instrument/scale/definition utilised to categorise and grade AEs [1], for example MedDRA [3] or CTCAE [4] definition
	5) Article specifies time frame of surveillance of AEs [1]
	6) Article specifies whether and which early stopping rule was used for toxicity
	7) Article specifies whether recurrent events in the same patient are counted as separate or single events
	8) Article specifies which patients were evaluable for toxicity -> Which dataset was used for safety analysis?
Results	9) Article reports reasons for treatment discontinuation
	10) Article reports whether deaths related to AEs [1] occurred
	11) AE [1] representation shown via graphs
	12) Article reports absolute numbers of AEs [1] (rather than percentages alone)
	13) Article does not only report AEs [1] observed above a certain frequency or rate cut-off (for example > 5% or 10% of participants)
	14 i) Article shows AEs [1] in different severity grades 14 ii) Article does not combine AEs [1] of varying severity
Discussion	15) Article does not use generic or vague descriptors of toxicity, such as „the regimen was generally well tolerated“
	16) Both benefits and harms are equally addressed
Extra Point	17) Conducting statistical tests and interpretation of test results

There is no point on subgroup analyses done because these are not parts of publications chosen via criteria in chapter 3.1. [1] AE: adverse event; [2] SAE: serious adverse event; [3] MedDRA: Medical Dictionary for Regulatory Activities; [4] CTCAE: Common Terminology for Adverse Events

This table shows the safety recommendations according to which the 33 articles are examined. The first 16 refer purely to the presentation of harms in publications and are divided into the parts Title/abstract, Introduction, Methods, Results and Discussion of a publication. They are derived from the recommendations of the journals and the recommendations of the CONSORT group. The seventeenth point relates to the performance of statistical tests and the interpretation of results. This is dealt with separately, as there are no recommendations.

As can be seen in Table 2, for each section of the publication there is at least one item which checks the part for the presentation on harms representation. Eligible publications will be evaluated for each of the 17 AE reporting elements in the main text or supplemental documents. The more reporting elements a paper takes into account, the better the AE representation of this publication is. For every article the sum is made, with every fulfilled element counting as one point. It should be noted that most of the items are related to the presentation of results, which also takes up the largest part of the publication. Many elements to be checked come from the CONSORT extension statement and are therefore not looked at again.

However, two elements are assessed in a split manner. On the one hand, it is a question of reporting AEs only above a certain frequency. If possible, all AEs should be reported in the publications, since rare adverse events can also play an important role in the assessment of a drug's safety. Therefore, element 3 i) checks whether the article says that all AEs were reported or just a selected sample. If only a sample is reported in the publication, then the cut-offs or grouping criteria should be presented. In element 3 ii) it is then checked whether there is a justification for the chosen cut-offs or grouping criteria. Similarly, reasons for different criteria used for AEs or SAEs should be explained. Element 3) is only considered to be completely fulfilled if condition 3 i) states that all AEs were reported or, if not, there has to be an explanation as stated in element 3 ii). If only condition 3 i) is given and just a sample is reported, this element is considered half-fulfilled, which means it is included in the sum of fulfilled elements with the value 0.5. On the other hand, the presentation of AEs by severity, which is represented by element 14), is also considered in two parts. In the first part, it is examined whether AEs are presented according to different degrees of severity, up to grade 5 toxicity and deaths. It is precisely the severity of an occurring AE that is an indicator of the danger of new treatment methods. In addition, it is investigated whether AEs of different severity levels are grouped together. AEs should be presented separately according to severity in order to show how many severe side effects occur. This element is also only considered fulfilled if both parts of it are fulfilled. If only element 14 i) is fulfilled, it is considered half-ful-

filled and is included in the sum of fulfilled elements with the value 0.5. If other elements are only partially fulfilled, then these also only count towards the total with the value 0.5. This is especially true for element 16) if the harms are only briefly addressed in one or two sentences in the discussion section of the publication. Furthermore, this rule is also applied for element 6) because there was no explicit explanation of the rule but it was said that a rule exists.

In addition to the recommendations from the CONSORT group and the journals, element 17) was included as a point from open questions remaining, from chapter 2.3. This concerns the performance and presentation of statistical tests and their results in publications. It is particularly relevant because statistical decisions are often made on the basis of test results. For example, one could test whether there is a difference in the number or severity of AEs occurring in the different study cohorts. The test results could provide an indication of whether a method shows significantly fewer side effects and could therefore be considered safer. However, there is the major problem of the power of the tests. There are usually not enough participants in a study to get a sufficiently high power for generally valid statements. There is also the problem of multiple testing. Since it is relevant to see how these problems are dealt with in tests, this point is additionally examined in the papers. The main aim is to see whether tests are carried out at all and, if so, how the above-mentioned difficulties are dealt with. As a last point it is necessary to say that “one recommendation from the CONSORT extension statement, describe any subgroup analyses and exploratory analyses for harms, was not included because this reporting element would only apply to the subset of trials that included such subgroups.”[3] If one article fulfilled all criteria, it would get 17 points, one for each complete fulfilled criterion.

3.3 Differences between recommendations and implementation in publications

In chapter 3.1, 33 articles were found, which will be analysed according to the criteria defined in chapter 3.2. This analysis will be carried out in the following according to several points of view.

3.3.1 General analysis

Firstly, all papers collectively are analysed. As shown in chapter 3.2, the elements 3), which deals with the sample of recorded AEs, and 14), which deals with severity grades, are divided into two points each, whereby each point is included in the sum with the value 0.5. Table 3 displays the absolute numbers of papers which meet a criterion as well as percentage value.

Table 3: Proportion of articles addressing each of the 17 AE reporting elements (N=33)

Reporting elements	No. of articles [n (%)]
1) Title or abstract states whether AEs [1] are addressed in study	25 (76%)
2) Introduction states whether benefits and AEs [1] are addressed in study	12 (36%)
3 i) Article specifies whether reported AEs [1] encompass all the recorded events or just a selected sample. 3 ii) If cut-offs/groupings are done, chosen cut-off/grouping criteria are explained. Reasons for different cut-offs used for AEs, SAEs,... explained?	24 (73%) 0 (0%)
4) Article specifies instrument/scale/definition utilised to categorise and grade AEs [1], for example MedDRA [3] or CTCAE [4] definition	23 (70%)
5) Article specifies time frame of surveillance of AEs [1]	21 (64%)
6) Article specifies whether and which early stopping rule was used for toxicity	12 (36%)
7) Article specifies whether recurrent events in the same patient are counted as separate or single events	1 (3%)
8) Article specifies which patients were evaluable for toxicity -> Which dataset was used for safety analysis?	22 (67%)
9) Article reports reasons for treatment discontinuation	21 (64%)
10) Article reports whether deaths related to AEs [1] occurred	23 (70%)
11) AE [1] representation shown via graphs	2 (6%)
12) Article reports absolute numbers of AEs [1] (rather than percentages alone)	4 (12%)
13) Article does not only report AEs [1] observed above a certain frequency or rate cut-off (for example > 5% or 10% of participants)	3 (9%)
14 i) Article shows AEs [1] in different severity grades 14 ii) Article does not combine AEs [1] of varying severity	23 (70%) 0 (0%)

15) Article does not use generic or vague descriptors of toxicity, such as „the regimen was generally well tolerated“	25 (76%)
16) Both benefits and harms are equally addressed	30 (91%)
17) Conducting statistical tests and interpretation of test results	3 (9%)

[1] AE: adverse event; [2] SAE: serious adverse event; [3] MedDRA: Medical Dictionary for Regulatory Activities; [4] CTCAE: Common Terminology for Adverse Events

This table shows the results of the article analysis according to the safety recommendations from Table 2. It shows how many of the 33 articles address at least one point of the recommendations in absolute numbers as well as in percentages.

In addition the criteria 6) and 16) have a special evaluation. For criterion 6), all papers that state that there is a stopping rule are listed, but those publications are only included in the total with a value of 0.5. Similarly, criterion 16) lists all papers that present both benefits and harms, although publications that do not present both in a balanced ratio, as required, are only included in the total with a value of 0.5 in sum, but this is not represented in Table 3. With these two specially treated criteria and the splitting of criteria 3) and 14), the result is that an article deals with an average of 7.18 [0;10.5] (SD = 2.2381) of the 17 criteria.

Furthermore, a criterion is taken into account on average by 14.00 [0;30] (SD = 9.0603) of the 33 articles, which can be seen in Figure 2.

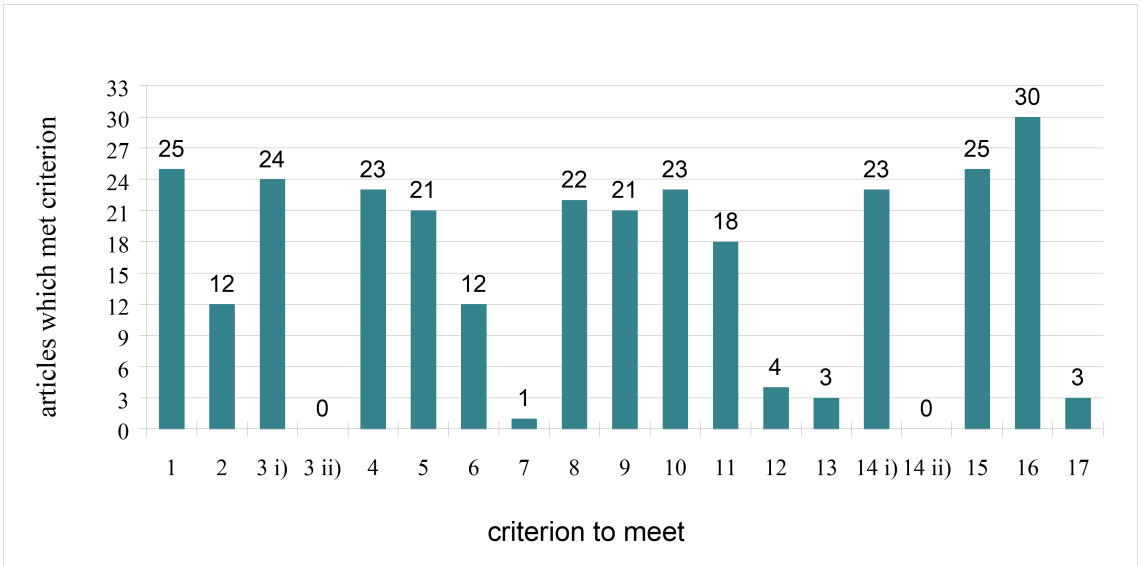

Figure 2: Number of articles meeting a criterion

This figure shows the number of articles that fulfil a criterion. The y-axis shows the number of articles that met the criterion. The x-axis shows the number of criterion analyses. The criterion met by most articles, 30 of 33, is criterion 16). The criteria 3 ii) and 14 ii) are the ones met by no article.

These two values show that, on average, not even half of the criteria are taken into account by an article. In Table 3 the number of items in percent that meet a criterion can also be seen.

The relative representation shows the differences between the criteria particularly well. Here the individual criteria are going to be examined and it will be shown how well they are fulfilled. The first two criteria are fulfilled very differently, although they are very similar. While approximately three quarters of the articles state in the title or abstract that harms are addressed in the publication, only a third state this in the introduction, although it should be addressed in both parts. In the methods section of the publication, it is particularly noticeable that the points for which an explanation must be provided are taken into account much less in the publications than points for which something should only be listed. This can be seen especially clearly in the case of criteria 3 ii), 6) and 7) in Table 3. Criteria 3 ii), which examines whether reasons for cut-offs are explained, and 7), which explains why recurrent AEs are reported per patient or per event, are not addressed by any article, while criterion 6), which examines whether an early stopping rule exists and is explained, is addressed by 12 articles. However, none of the articles explain the rule in more detail, which should be done. In contrast, criteria 3 i), which says whether AEs are reported as a sample or not, 4), which AE definition is used, 5), in which time period AEs are recorded, and 8), on which dataset AEs are reported, are considered much more frequently in the publications. This is because they ask for definitions of certain presentations, such as the time period in which the AEs are observed or the way in which they are presented. These criteria are taken into account by more than 20 articles each, which means approximately 70 percent per criterion.

In the area of results, there are also clearly recognisable differences in the presentation of the criteria in the publications. While both the indication of reasons for treatment discontinuation and the indication of deaths due to AEs are taken into account by 21 and 23 articles, respectively, and are thus frequently reported, the AEs are mostly only reported above a defined cut-off. Only three papers report all observed AEs in the publication and not only frequently occurring AEs, as can be seen in criterion 13). In the other 30 articles, all AEs are not reported in the supplemental material either. Furthermore, only four papers also report the absolute number of AEs and not only the number of persons who had at least one AE. This means that important information about the frequency of AEs is lost, as recurrent AEs are counted just as often as AEs that occurred

only once. It can also be seen that in only two cases AEs are presented graphically in addition to being tabulated, which can be seen in element 11) of table 3. The last criterion examined in this part of the publication is whether different severity grades of AEs are represented. This is the case in 70% of the papers, as can be seen in element 14 i), but all papers combine AEs of different severities, i.e. for example only the number of at least grade 3 AEs is given, but not separated into grades 3, 4 and 5 AEs. This division plays an important role in the assessment of the individual AEs, as it makes a decisive difference for a patient whether they have to go to hospital for a check-up (grade 3 AE) or whether an AE is life-threatening (grade 4) or leads to death (grade 5). For this reason, different severity grades of AEs should not be indicated cumulatively.

Criteria 15) and 16), which deal with the discussion part of the publications, perform very well in comparison. In over 90 percent of the papers, both benefits and harms are addressed, although in some papers the benefits are clearly prioritised. Furthermore, in almost three quarters of the papers, a vague description of the safety profile is dispensed with, although even more care should be taken to avoid vague expressions.

As a separate point, which includes element 17), statistical tests will be investigated. Although statistical tests are carried out in a total of 26 out of 33 papers, these only refer to AEs in three cases. In the other 23 cases, tests are only carried out on primary endpoints, which means mostly on the efficacy of a new medication or the general survival up to a certain time point. This mostly owes to the fact that an adjustment due to the multiple testing problem is not useful for testing for AEs, since the power of the tests is not large enough to be able to make general statements from significant results. Nevertheless, in addition to descriptive analysis, it would be a possibility to check whether the safety profile differs significantly between the different groups. However, it is understandable that these statements, which cannot be interpreted well, are not made in the publications.

In summary, some criteria are quite well taken into account in the publications, namely by at least 60% of the papers. These include criteria 1), 3 i), 4), 5), 8), 9), 10), 14 i), 15) and 16). Criteria 2) and 6) are regularly met, i.e. by 30% to 60% of the papers, but they should be taken into account even more frequently and the explanations in particular should be included even more often. Some criteria are only rarely or not at all presented by the papers, i.e. by not even 30% of the publications. These include the elements 3 ii), 7), 11), 12), 13) and 14 ii), as well as the element of statistical tests, since so far mostly

only primary endpoints are tested, but rarely for AEs. In the future, these criteria must be taken into account even more frequently in publications of phase 3 clinical trials.

3.3.2 Analysis of differences between the journals

After examining all the articles together at the beginning, in this part the differences between the two journals NEJM and The Lancet will be analysed. First, a closer look is taken at the 14 articles from the NEJM, which are also shown in Figure 3a.

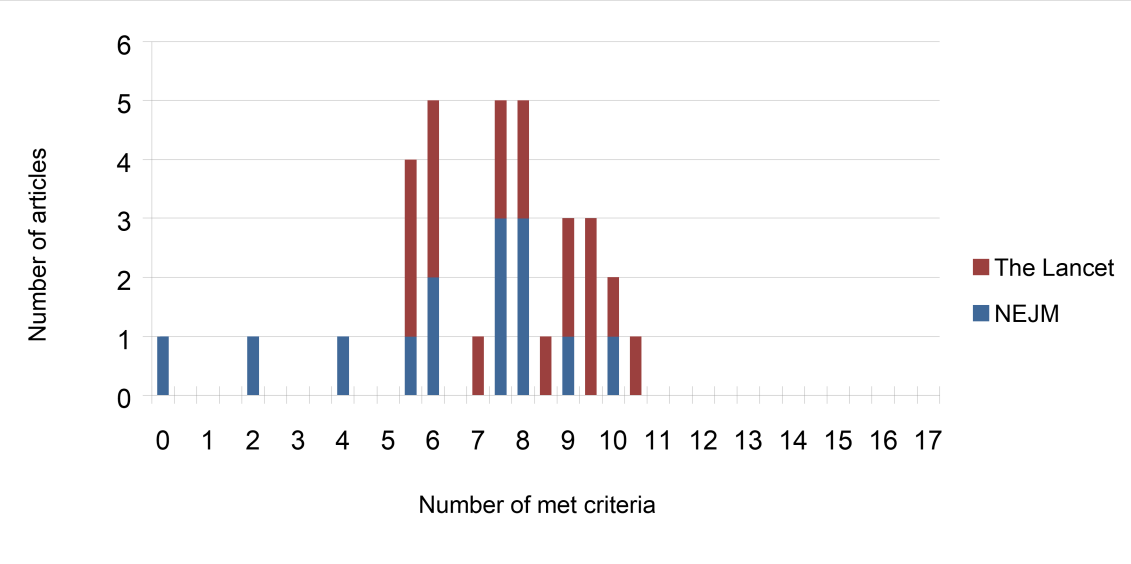

Figure 3a: Number of met criteria per article and journal

This figure displays the number of fulfilled criteria per article from the New England Journal of Medicine in blue and The Lancet in red. The x-axis shows the sum of met criteria. On the y-axis the number of articles meeting this amount of criteria is given. This sum is calculated as described in chapter 3.2. The article that scores highest fulfils 10.5 of the 17 criteria and is from The Lancet. The item with the lowest score does not fulfil any of the criteria and is from NEJM.

On average, an article fulfils 6.36 [0;10] (SD = 2.6486) criteria. The range extends from no fulfilled criterion by the article ”Lobar or Sublobar Resection for Peripheral Stage 1A Non-Small-Cell Lung Cancer”[21], up to ten fulfilled criteria by the article ”Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B”[14]. It is notable that most articles fulfil between 5.5 and 8 criteria in total. These can be separated in two groups where one group is containing three articles which fulfil 5.5 to 6 criteria and the other group is containing six articles which fulfil 7.5 to 8 criteria. In addition, there are some clear outliers at the top and bottom. At the top, there is the one article just mentioned

above with ten fulfilled criteria as well as article 13 with nine fulfilled criteria. At the bottom the article with no fulfilled criterion, as well as two other articles, out of which one only fulfilled two and one only four criteria.

Now a closer look is taken at the ten articles from The Lancet together with nine articles from the subcategory The Lancet Oncology. These fulfil on average 7.79 [5.5;10.5] (SD = 1.6329) criteria per article, which is about 1.5 criteria more per article than in the NEJM articles. Furthermore, the margin between the article with the most and least fulfilled criteria is also much smaller here. The three articles "Health-related quality of life and neurocognitive functioning with lomustine-temozolomide versus temozolomide in patients with newly diagnosed, MGMT-methylated glioblastoma (CeTeG/NOA-09): a randomised, multicentre, open-label, phase 3 trial"[40], "Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study"[43] and “Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial”[47] with 5.5 fulfilled criteria are the ones that fulfil the fewest criteria. With a total of 10.5 criteria fulfilled out of 17 possible criteria, the article "Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial"[48] is the overall best-performing article. Unlike in the NEJM, there are no large margins, i.e. more than one point per fulfilled criterion, between the individual scores of the articles examined here.

Now that it is clear that the NEJM takes fewer criteria into account than The Lancet, it is interesting to see which criteria show the most differences. This is shown in Figure 3b.

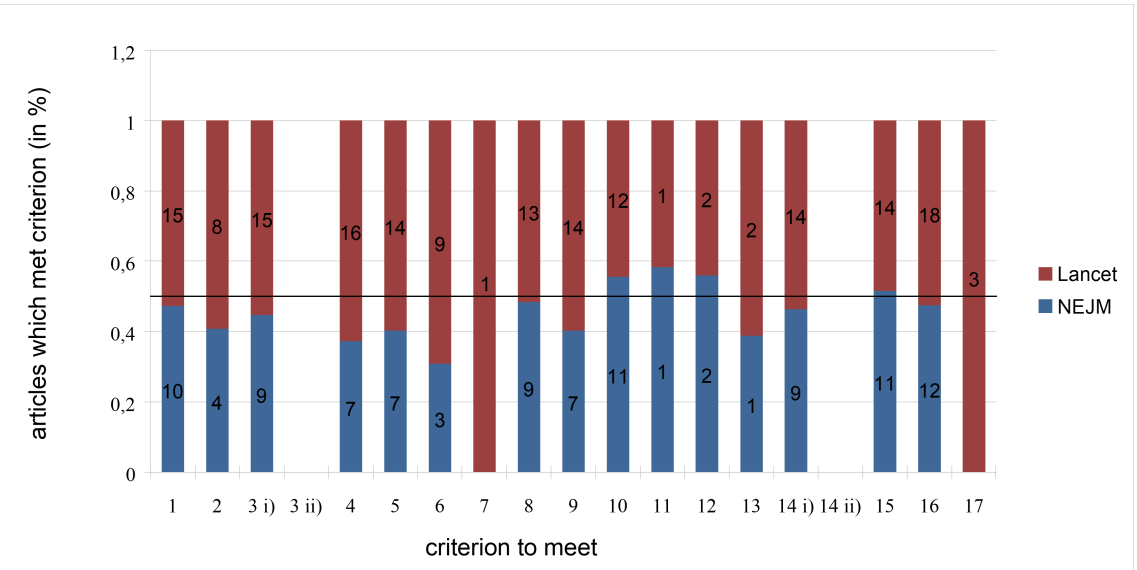

Figure 3b: Differences in fulfilled criteria between NEJM and The Lancet

This figure shows the proportion of fulfilled criteria per journal. For each journal, the proportion of articles that fulfil a criterion is calculated. This is necessary because a different number of papers from the two journals were examined due to the selection criteria of the papers. If the same proportion of articles fulfil the criterion for both journals, the bars meet at the value 0·5 in the figure. The articles of the journal that proportionally fulfil more criteria have the larger bar. However, the absolute numbers of items that fulfil a criterion are indicated in the bars, as this allows one to additionally see how often a criterion has been fulfilled per journal.

Figure 3b shows the proportion of fulfilled criteria per journal. For each journal, the proportion of articles that fulfil a criterion is calculated. This is necessary because a different number of papers from the two journals were examined due to the selection criteria of the papers. If the same proportion of articles fulfil the criterion for both journals, the bars meet at the value 0.5 in the figure. The articles of the journal that proportionally fulfil more criteria have the larger bar. However, the absolute numbers of items that fulfil a criterion are indicated in the bars, as this allows one to additionally see how often a criterion has been fulfilled.

It is noticeable that for almost all criteria, the publications from the journal The Lancet perform better than those from the NEJM. Only for the four criteria 10), reporting of deaths, 11), AE representation via graphs, 12), reporting of absolute AE numbers, and 15), no use of vague descriptions for toxicity, the papers from the NEJM perform slightly better. For all other criteria, the papers from The Lancet perform better, in some cases clearly better. This is particularly striking for criteria 4), definition for AE given, 5), time period of recording AEs specified, 6), given early stopping rule for toxicity, 9) reporting of treatment discontinuations, and 13), not only reporting AEs above a frequency cut-off, as well as for criteria 7), specifies dealing with recurrent events per patient, and 17), implementation of statistical tests, which were only addressed by papers from The Lancet. Nevertheless, the difference in these two criteria between the journals is not as clear as can be assumed from Figure 3b, since they were fulfilled only once and three times, respectively, in papers from The Lancet.

In summary, the criteria for the presentation of AEs are taken into account much better by papers in The Lancet than in the NEJM. One reason for this could be that some criteria, such as the existence of a stopping rule, criterion 6), are needed more often in on-

cology studies. Since there are proportionately more oncology studies in the papers from The Lancet, this could be a reason why the NEJM papers perform worse. Nevertheless, both journals should pay even more attention to orientating the presentation of AEs even more towards the recommendations.

3.3.3 Differences between papers on oncology and those on other topics

After the differences between the two journals have been examined, a closer look will be taken at the differences between papers from oncology and papers that deal with other topics. This comparison is particularly interesting because in Chapter 4 the AE representation of a study from oncology will be examined. Firstly, the consideration of recommendations in the 19 oncology papers is investigated, which are shown in Figure 4a.

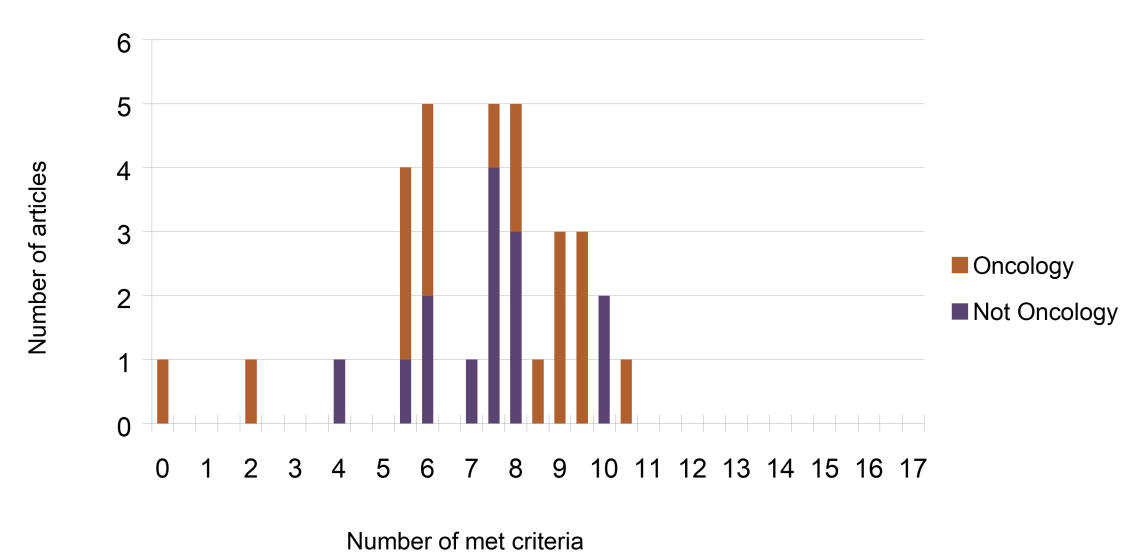

Figure 4a: Number of met criteria per article and medical field

This figure displays the number of fulfilled criteria per article from the medical field oncology in orange and from other topics in violet. The x-axis shows the sum of met criteria. On the y-axis the number of articles meeting this amount of criteria is given. This sum is calculated as described in chapter 3.2. The article that scores highest fulfils 10.5 of the 17 criteria and is from the medical field oncology. The item with the lowest score is also from the medical field oncology and does not fulfil any of the criteria.

First, a closer look will be taken at the oncology paper. On average, an article fulfils 7.08 [0;10.5] (SD = 2.6271) of the criteria. The article with the most fulfilled criteria, 48, as well as the one with the least fulfilled criteria, 21, are papers concerned with on-

cology. Furthermore, it can be said that the articles from oncology are divided into two areas with outliers at the top and bottom. In addition to the two articles just mentioned with the highest and lowest values, there is another outlier at the bottom that only fulfils two criteria, namely the article with the number 17. The two ranges in which the remaining articles are distributed lie on the one hand between 5.5 and 6 fulfilled criteria and on the other hand between 7.5 and 9.5 fulfilled criteria. The mean value of fulfilled criteria lies exactly in between and thus divides the articles from oncology into these two ranges.

Now it is compared how well the recommendations are taken into account in the 14 non-oncology papers. On average, a paper fulfils 7.32 [4;10] (SD = 1.5539) criteria. This is about 0.5 criteria per article less than in oncology. Nonetheless, the variance between the articles is significantly lower than in all other categories examined. The article with the number 20, which only fulfils four criteria, is the lowest-scoring article. The two highest-scoring articles, with ten out of 17 criteria fulfilled, are those with the numbers 14 and 35. Again, the remaining articles can be divided into two groups, but these have a much smaller range than the oncology papers. In one group, there are three articles that lie in the range of 5.5 to 6 fulfilled criteria. In the second group, eight articles lie in the range of 7 to 8 fulfilled criteria. Here the mean value lies in the group with the higher values because more articles are part of it.

Compared to the papers from oncology, the presentation of AEs in the articles is clearly more balanced. Overall, not even half of the criteria are fulfilled in both categories, as has already been shown in the previous chapters. However, unlike the differences between the journals, the differences between oncology and non-oncology papers are only very slight.

Since there are only minor differences here, a closer look is taken at how the differences between the criteria are distributed. This can be seen in more detail in Figure 4b.

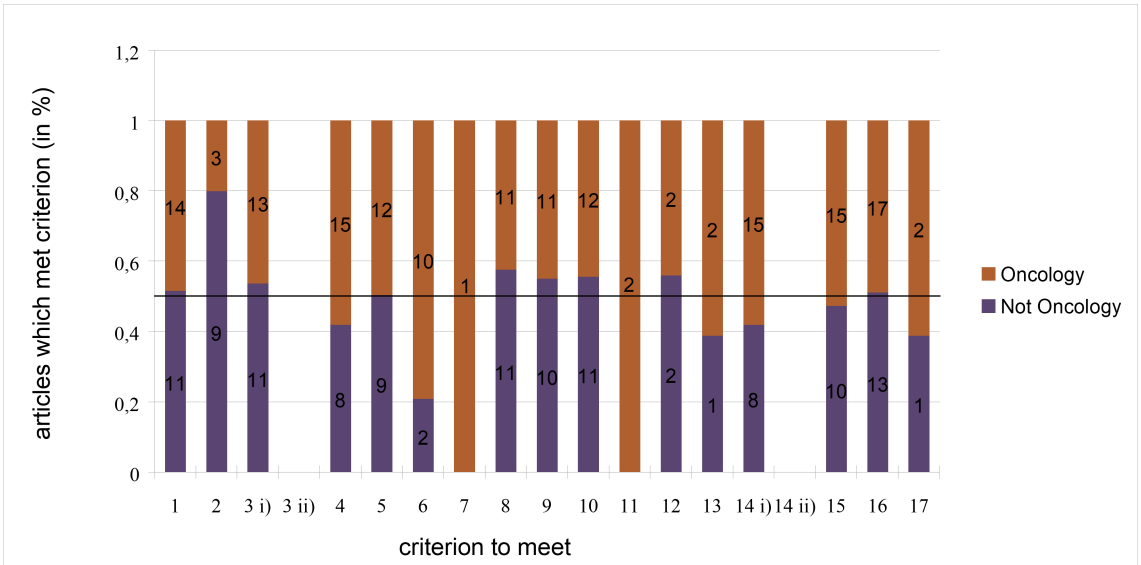

Figure 4b: Differences in fulfilled criteria between papers on oncology and those on other topics

This figure shows the proportion of fulfilled criteria per medical field. For each medical field, the proportion of articles that fulfil a criterion is calculated. This is necessary because a different number of papers from the two medical fields were examined due to the selection criteria of the papers. If the same proportion of articles fulfil the criterion for both disease categories, the bars meet at the value 0.5 in the figure. The articles of the medical field that proportionally fulfil more criteria have the larger bar. However, the absolute numbers of items that fulfil a criterion are indicated in the bars, as this allows one to additionally see how often a criterion has been fulfilled per medical field.

In the differences between the two categories it is very clear that some criteria are more closely considered by oncology papers and some by non-oncology papers. Especially elements 4), definition of AEs given, 6), early stopping rule given, 13), AEs not only reported above frequency cut-off, 14 i), different severity grades of AEs shown, and 17), implementation of statistical tests, are considered more carefully by the oncology papers compared to the non-oncology papers. Criterion 7), specifies dealing with recurrent events per patient, and criterion 11), AE representation via graphs, are seemingly taken into account more diligently, but there are only one respectively two papers from oncology and none from the rest of the papers that consider it. Therefore, no statement can be made for these criteria. Criteria 1), title abstract states whether AEs are addressed, 5), time period of recording AEs specified, 15), no use of vague descriptions for toxicity, and 16), which states whether benefits and harms are addressed equally in discussion, are treated approximately equally. In comparison, criteria 2), introduction states whether AEs are addressed, 3 i), states whether all recorded events are reported or not,

8), whether dataset for safety analysis is specified, 9), reasons for discontinuations are reported, 10), deaths are reported, and 12), absolute number of AEs are reported, are more closely considered by the non-oncology papers.

Overall, there are no major differences between the categories observed here, although there are some significant differences in some criteria. For all these criteria, more attention should be paid to taking them into account in the publications in the respective other category.

4. TRIANGLE trial

4.1 Introduction to TRIANGLE trial and data description

After looking at published papers and how they report AEs, data from the TRIANGLE trial are used to look at the impact of different analysis strategies on the representation of AEs.

First, a brief overview of the trial design is given. The trial deals with younger mantle cell lymphoma (MCL) patients and documents a new therapy with the medication Ibrutinib, which has already shown promising efficacy in relapsed MCL patients. This is the reason why the therapy is now also applied when the disease is first diagnosed. The current standard of care is a high-dose cytarabine-containing immunochemotherapy followed by autologous stem cell transplantation (ASCT) and Rituximab maintenance. The study is a "randomised, open label, 3-arm TRIANGLE trial to evaluate the addition of Ibrutinib to standard treatment (arm A+I) in comparison to the previous standard treatment (arm A) and an Ibrutinib-containing treatment without ASCT (arm I)."[1] All patients (n = 870) were randomised 1:1:1 to the three trial arms A (n = 288), A+I (n = 292), I (n = 290).

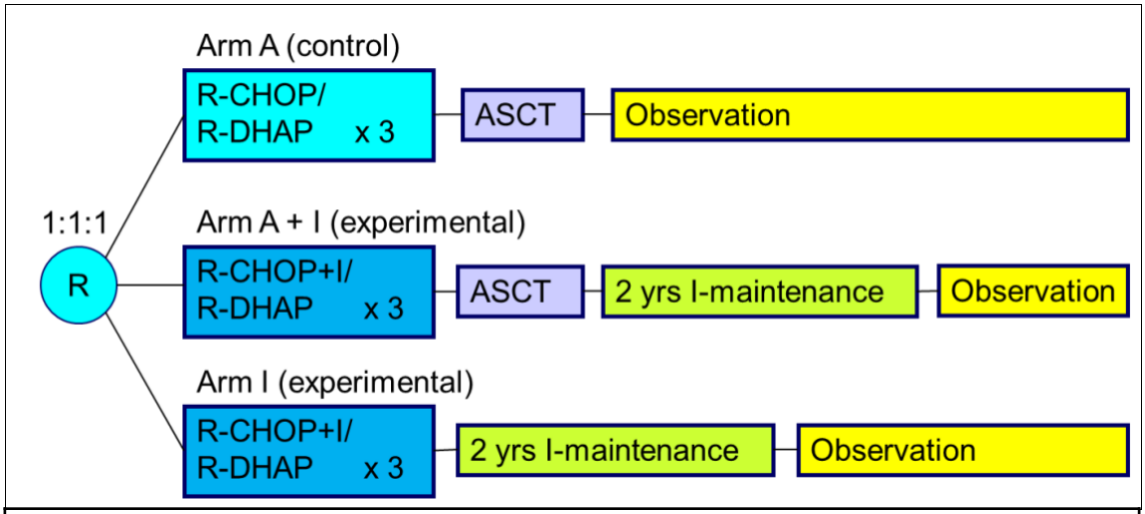

Figure 5: Trial design of TRIANGLE trial

This figure shows how the TRIANGLE study is structured. There are three treatment arms, which consist of different treatment methods. The study is a randomised, open label, 3-arm TRIANGLE trial to evaluate the addition of Ibrutinib to standard treatment (arm A+I) in comparison to the previous standard treatment (arm A) and an Ibrutinib-containing treatment without ASCT (arm I).

For all treatment arms the therapy starts with an immunochemotherapy. This phase is called induction. It lasts six times 21 days, with arms A+I and I each additionally receiving the new drug Ibrutinib. In arms A and A+I, ASCT follows the induction but is not carried out in arm I. In the two arms that already received Ibrutinib in the induction phase, a two-year maintenance therapy with Ibrutinib follows. The study is concluded through an observation of follow-up phase in each treatment arm (see Figure 5).

Data from the TRIANGLE trial on patients' AEs is given. This is the data from the electronic Case Report form (eCRF) on all AEs documented and coded according to MedDRA up to 22.05.2022. The different groups are defined according to therapy start, in terms of the AT dataset. Table 4 shows a brief excerpt of how the data are structured.

Table 4: Overview of TRIANGLE trial data

Patient ID	Period	Induction group	ASCT group	SOC [1] term reported	SOC [1] term reclassified
1	induction	R-CHOP/R-DHAP	R-CHOP/R-DHAP	Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders
9	asct	IR-CHOP/R-DHAP	IR-CHOP/R-DHAP	Injury, poisoning and procedural complications	Injury, poisoning and procedural complications
14	maintenance	IR-CHOP/R-DHAP	IR-CHOP/R-DHAP	Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders
17	asct	IR-CHOP/R-DHAP	IR-CHOP/R-DHAP	Infections and infestations	Infections and infestations
861	follow-up	R-CHOP/R-DHAP	R-CHOP/R-DHAP	Blood and lymphatic system disorders	Blood and lymphatic system disorders

PT [2] reported	PT [2] reclassified	Maintenance group	Grade	SAE [4]	AE [3] related to Ibrutinib	Onset date
Rhinorrhoea	Rhinorrhoea	A	1	0	N	24.08.2020
Lip injury	Lip injury	A+I	2	0	N	22.12.2020
Arthralgia	Arthralgia	I	3	0	Y	08.06.2020
Escherichia sepsis	Sepsis	NA	4	1	N	22.03.2021
Neutropenia	Neutrophil count decreased	A	3	0	N	20.12.2018

[1] SOC: System Organ Class; [2] PT: preferred term; [3] AE: adverse event; [4] SAE: serious adverse event

The table presents an overview of the dataset that has data on the patients' AEs. The dataset has 13 variables, all of which are represented in as character, except for the Patient ID, which is numeric. In total, there are 17120 entries in the dataset of 870 patients. The variables with the addition reported are recorded according to MedDRA and presented as stated by the physicians. The variables with the addition reclassified have been reclassified by central medical review at the trial sponsor according to CTCAE V.4.03, but only those AEs that occurred in at least ten patients.

The dataset consists of the 13 variables shown in Table 4. All variables are of type character except the Patient ID, which is numeric. It has a total of 17120 rows and therefore the same number of entries for AEs. If more than one AE occurs in a patient, each AE is recorded in a single row. Due to data protection, the different patients can only be identified by their ID. A total of 870 patients with IDs 1 to 870 are observed and their AEs are recorded. In addition to the AEs occurring during the different treatment phases, induction, ASCT, maintenance and follow-up, AEs before the start of the treatment are also recorded. As these cannot be related to the treatment, they are not taken into account here. AEs with the PT unknown are not taken into consideration either, as no statements can be made about them. These two exclusions result in a total of 15589 AEs that occurred during the entire study. Furthermore, the following points should be taken into account. There are two possible values for the variables induction group and ASCT group, which indicate the medication taken in the respective phase. On the one hand, there is the expression IR-CHOP/R-DHAP, which means treatment with the new drug Ibrutinib was given, and R-CHOP/R-DHAP, which means no treatment with the new drug Ibrutinib was given. The treatment arm, according to figure 5, to which a patient belongs is indicated in the variable maintenance group. The data on AEs is shown in the variables SOC term reported and SOC term reclassified, the AEs that occurred are presented according to system organ class (SOC), while in the variables PT reported and PT reclassified, they are presented according to preferred term (PT). The variables with the addition reported are recorded according to MedDRA and presented as stated by the physicians. The variables with the addition reclassified have been reclassified according to CTCAE, but only those AEs that occurred in at least ten patients. The reclassification was carried out because the MedDRA coding allows more PTs and the CTCAE coding also assigns diseases more stringently to the respective organs. The reclassification attempts to avoid that certain PTs according to CTCAE are not found among the more frequent ones, as they are distributed among several PTs according to MedDRA. In the first instance, however, only the PTs were reclassified, but not the SOCs. This initially led to the problem that the same PTs could be found in different SOC terms. However, since the PTs are clearly assigned to a SOC term according to CTCAE V.4.03, all SOCs also had to be reclassified. For all PTs that occurred in different SOC terms, the SOC reclassified variable was adapted by hard coding.[1] Although all multiple PTs are reclassified in the SOC, some PTs that have not been reclassified, as they were so rare, may

[1] see R program „Tabellen neu mit Hardcode.Rmd“

also be incorrectly assigned in the SOC, as they would otherwise be assigned to a different SOC term after reclassification. This can lead to problems in the frequency of AEs occurring, which cannot be avoided. In the variable Grade, the severity of the AE is shown, according to CTCAE from grade 1 to grade 5. In the variable SAE, shown with 0-1 coding, it is indicated whether the AE is a SAE (1) or not (0). AE related to Ibrutinib records whether or not the AE is related to the drug being tested, Ibrutinib. Y indicates that there is a connection, N indicates that there is no connection. The variable onset date indicates the date on which the AE first occurred in the data value format of Excel. This serves the purpose of listing the occurring AEs in a chronological order.

4.2 Showing adverse event evaluation possibilities through data of TRIANGLE trial

After looking at how the trial was conducted and how the available data is structured in chapter 4.1, it is attempted to create an analysis of the harms that is as close as possible to a perfect analysis according to the criteria examined in chapter 3.2. The analysis is limited to the methods and results sections, as the objective is to show just the statistical methods and analysis as well as the presentation of results.

4.2.1 Attempt at getting a perfect harms analysis

In this first part, the aim is to show how all the criteria examined in Chapter 3 can be represented with the TRIANGLE trial data. To begin with, the criteria 3) to 8), which are assigned to the methods section of the publication, are analysed.

First, as required in criterion 3), it is specified whether all AEs are reported or only a sample and what the reasons are for this. All AEs are reported by phase and severity grade in the appendix. In the intext tables only AEs which were observed in at least 2.5% of patients per phase are reported, as well as SAEs that are related to the new drug by severity grade. The frequency cut-off is used in the text because there are a very high number of AEs in the study. This cut-off was chosen because there were a lot of AEs and not all can be represented in text. Recurrent events are counted as separate events as well as individual events if they occur more than once in a patient. This should also be indicated, as can be seen in criterion 7). No statement can be made about an existing stopping rule due to toxicity, criterion 6), as no information is available on this. The evaluation of the AEs was carried out according to the reclassification described in Chapter 4.1 with the definitions according to CTCAE, as specified in criterion 4). However, two problems have to be taken into account. Since the reclassification was only carried out manually, only those PTs that occurred at least ten times were reclassified due to limited resources. Furthermore, the SOC was not reclassified. This was only done afterwards by hard coding the PTs assigned to two SOC terms. Now it is looked at the combined criteria 5) and 8). The data of the AEs were divided into the four phases of the study, induction, ASCT, maintenance and follow-up, as can be seen in Figure 5. The duration of the individual phases varies according to the treatment arm or is non-existent. The AEs are analysed on the AT dataset, which is redefined for each phase. For

the induction phase, the AT dataset is defined for all patients who started the induction. This is divided into the two treatment groups IR-CHOP/R-DHAP, treatment with Ibrutinib, and R-CHOP/R-DHAP, treatment without Ibrutinib. For the ASCT phase, it is defined for all patients who have undergone induction and then started high dose treatment. Here, there is the same division as in the induction phase for the treatment groups. For the maintenance and follow-up phases, patients are divided into three groups. Group A is defined as patients who started induction with R-CHOP/R-DHAP and high-dose treatment and did not start Ibrutinib maintenance, group A+I as patients who started induction with IR-CHOP/R-DHAP and high-dose treatment and Ibrutinib maintenance and group I as patients who started induction with IR-CHOP/R-DHAP, did not start high-dose treatment and started Ibrutinib maintenance. The maintenance and follow-up phases are analysed jointly. This is because there is no Ibrutinib maintenance phase in treatment group A. However, there is also maintenance with Rituximab and some centres have assigned AEs to this maintenance phase, although this should not be the case. The analysis of the AEs always takes place on the AT dataset valid for the respective phase.

After looking at the criteria of the methods section, this part will be concluded by examining the criteria of the results section, which means criteria 9) to 14).

First of all, treatment discontinuations due to AEs as well as deaths should be reported, as shown by criteria 9) and 10). Since no treatment discontinuations are shown in the available data and no reasons are given for them, they cannot be reported. A total of 35 deaths due to AEs occurred in the TRIANGLE trial, which means that the occurring AE was of grade 5. The deaths can be seen in Table 5.

Table 5: Deaths occurred in TRIANGLE trial

Patient ID	**Period**	**AE[1] by SOC[2]**	**AE[1] by PT[3]**	**Treatment group**
174	induction	Infections and infestations	Lung infection	R-CHOP/R-DHAP
177	induction	Psychiatric disorders	Completed suicide	IR-CHOP/R-DHAP
229	induction	Gastrointestinal disorders	Diarrhea	R-CHOP/R-DHAP
442	induction	Gastrointestinal disorders	Melaena	R-CHOP/R-DHAP
466	induction	Infections and infestations	Lung infection	IR-CHOP/R-DHAP
29	asct	Infections and infestations	Sepsis	R-CHOP/R-DHAP
33	asct	Gastrointestinal disorders	Anal fistula	R-CHOP/R-DHAP
44	asct	Infections and infestations	Sepsis	R-CHOP/R-DHAP
73	asct	Gastrointestinal disorders	Gastric haemorrhage	IR-CHOP/R-DHAP

85	asct	Blood and lymphatic system disorders	Platelet count decreased	IR-CHOP/R-DHAP
144	asct	Infections and infestations	Corona virus infection	IR-CHOP/R-DHAP
189	asct	General disorders and administration site conditions	Sudden death	R-CHOP/R-DHAP
194	asct	Infections and infestations	Lung infection	IR-CHOP/R-DHAP
446	asct	Respiratory, thoracic and mediastinal disorders	Adult respiratory distress syndrome	IR-CHOP/R-DHAP
494	asct	Blood and lymphatic system disorders	Bone marrow hypocellular	R-CHOP/R-DHAP
494	follow-up	Vascular disorders	Venoocclusive disease	A
512	asct	Respiratory, thoracic and mediastinal disorders	Pneumonitis	R-CHOP/R-DHAP
512	asct	Nervous system disorders	Hemiparesis	R-CHOP/R-DHAP
531	asct	Infections and infestations	Sepsis	R-CHOP/R-DHAP
629	asct	Infections and infestations	Lung infection	IR-CHOP/R-DHAP
701	**asct**	**Infections and infestations**	**Sepsis**	**IR-CHOP/R-DHAP**
790	asct	Infections and infestations	Upper respiratory infection	IR-CHOP/R-DHAP
842	asct	Infections and infestations	Sepsis	IR-CHOP/R-DHAP
850	asct	Infections and infestations	Corona virus infection	R-CHOP/R-DHAP
70	maintenance	Infections and infestations	Infections and infestations - Other, specify	A + I
287	maintenance	Cardiac disorders	Myocardial infarction	I
342	maintenance	Infections and infestations	Corona virus infection	I
356	maintenance	Infections and infestations	Corona virus infection	A
704	maintenance	Infections and infestations	Corona virus infection	A + I
403	follow-up	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Neoplasms benign, malignant and unspecified (incl. cysts and polyps) - Other, specify	A
429	follow-up	Infections and infestations	Severe acute respiratory syndrome	A
590	follow-up	Infections and infestations	Corona virus infection	NA
615	follow-up	Infections and infestations	Corona virus infection	I
640	follow-up	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Small cell lung cancer	NA
658	follow-up	Infections and infestations	Sepsis	A
678	follow-up	Respiratory, thoracic and mediastinal disorders	Tracheal inflammation	A + I
749	**follow-up**	**Neoplasms benign, malignant and unspecified (incl. cysts and polyps)**	**Malignant melanoma**	**A + I**

[1] AE: adverse event; [2] SOC: System organ class; [3] PT: preferred term

This table lists all patients who died due to an AE. This means that the AE was of grade 5. All AEs that are considered related to the drug Ibrutinib are marked in bold. The patient ID is the phase to which the AE belongs, with the treatment group to which the patient belongs in this phase. In addition, the SOC and PT term of the AE are given. A total of 35 patients died. For two patients, IDs 494 and 512, two AEs were reported as the reason for death and therefore both are shown here in the table.

As can be seen in table 5, a total of 35 patients died from AEs. They are listed here with their patient ID. In addition, the SOC and PT term is given according to which the AEs that led to death were reported. The phase of the study in which the patient was when the AE occurred is also indicated, as is the treatment group of the AT dataset in this phase. For two patients, two AEs were reported that led to death. This is the case for the patients with IDs 494 and 512. Furthermore, it is noticeable that by far the most deaths occur in the ASCT phase, namely almost half of them with 17 out of 35 deaths. Also, only two of the deaths are attributable to the new drug Ibrutinib. One of these is the death of patient 701 in the ASCT phase, who developed sepsis. The other is the death of patient 749 in the follow-up phase, in which a malignant melanoma occurred. The criteria 11), representation of AEs via graph, 12), AEs are reported with absolute numbers, 13), not only reported above a certain frequency cut-off, and 14), AEs given in different severity grades, are taken into account in the evaluation of the results. This happens smoothly and merges into one another, which is why it is no longer indicated individually which criterion is fulfilled. Criterion 13) is only fulfilled in the appendix but not in the in text tables because of the huge amount of occurring AEs. First, it is looked at the SAEs caused by the new drug Ibrutinib at all phases. The phases maintenance and follow-up are combined, since the maintenance phase does not exist for treatment group A. To begin with, the occurrence of the AEs according to SOC in the treatment phases induction and maintenance will be compared, which are shown in figures 6a and 6b.

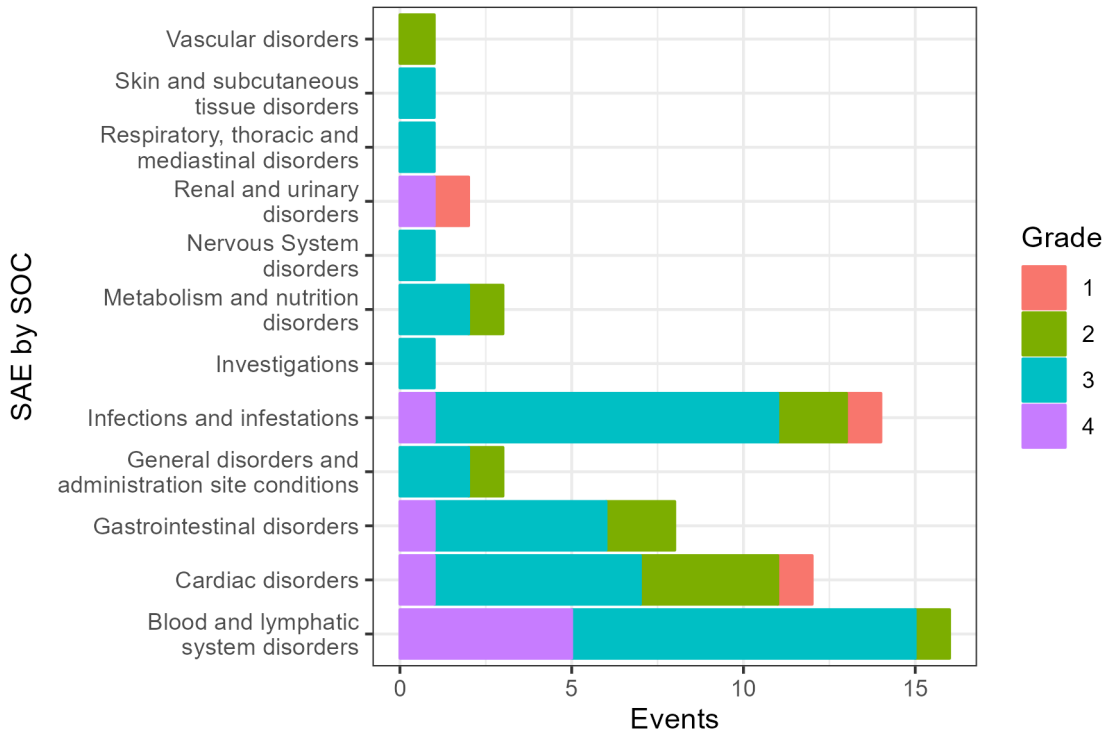

Figure 6a: SAEs related to Ibrutinib in induction phase by SOC

This figure shows all SAEs by grade that are related to the new drug Ibrutinib according to SOC in induction phase. The number of events is plotted on the x-axis, the different SOC categories on the y-axis. For every SOC term the division according to the grades is displayed. It can be seen that the categories Blood and lymphatic system disorders, Infections and infestations, Cardiac disorders and Gastrointestinal disorders occur most frequently.

Figure 6a shows that SAEs related to Ibrutinib occur in a total of 12 SOC terms in the induction phase. In the three categories Blood and lymphatic system disorders, Infections and infestations and Cardiac disorders, they even occur more than ten times. In addition, it can be seen that the most SAEs were of grade 3.

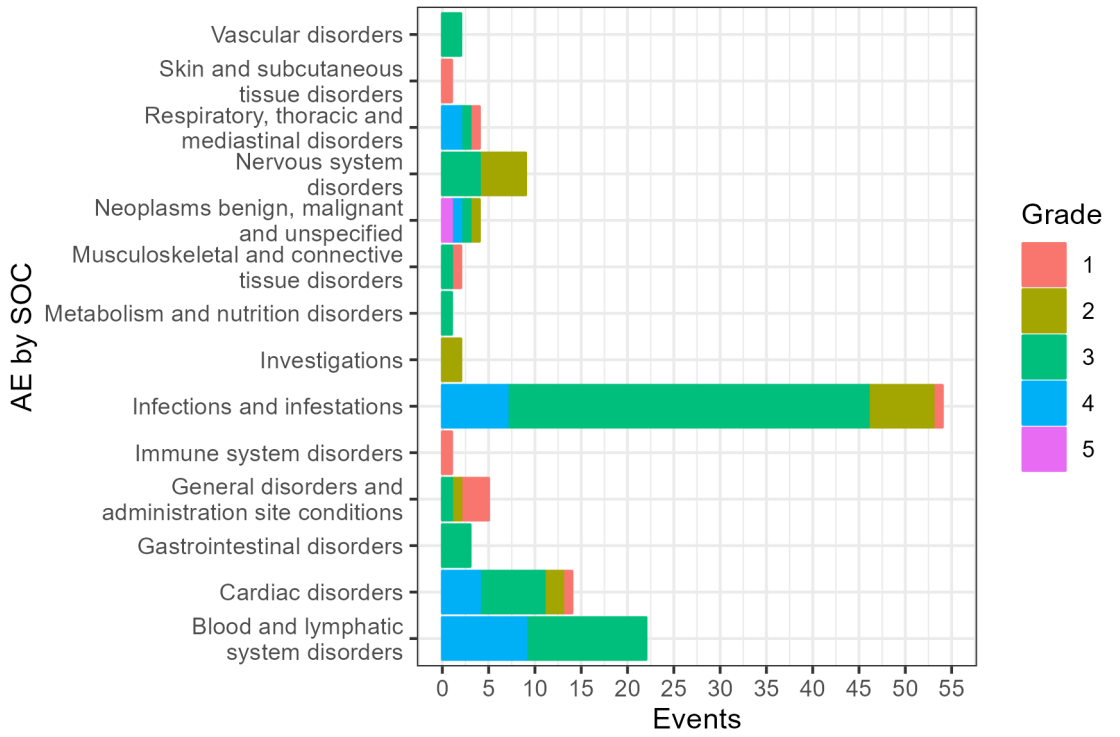

Figure 6b: SAEs related to Ibrutinib in maintenance and follow-up phase by SOC

This figure shows all SAEs that are related to the new drug Ibrutinib according to SOC in maintenance and follow-up phase. The number of events is plotted on the x-axis, the different SOC categories on the y-axis. For every SOC term the division according to the grades is displayed. It can be seen that the term Infections and infestations occurs most often, followed by the terms Blood and lymphatic system disorders and Cardiac disorders.

Figure 6b shows that SAEs related to Ibrutinib occur in a total of ten SOC terms in the maintenance phase. In the three categories Blood and lymphatic system disorders, Cardiac disorders and Infections and infestations, they even occur more than ten times. By far the most SAEs are in Infections and infestations with 54 occurring SAEs.

In the graphs, only the induction phase and combined maintenance/follow-up phase are shown, as the drug Ibrutinib is only administered in these phases.

Now it is looked at the distribution of SAEs that are related to Ibrutinib according to their severity. This distribution is divided into individual phases and can be seen in tables 6a to 6c. The tables show the SAEs related to Ibrutinib, according to SOC, PT and severity, both the number of events that occurred and the number of patients in whom such an SAE occurred as absolute and as percentage value. The tables are sorted first by

number of patients, then by number of events. The PT terms are assigned to the respective SOC term and the severity levels are given for each term.

Table 6a: SAEs related to Ibrutinib in induction phase

SAEs [1] related to Ibrutinib by SOC [2], PT [3] and Grade	Overall events	(N = 587)	%
Blood and lymphatic system disorders	**16**	**16**	**3%**
2	1	1	0%
3	10	10	2%
4	5	5	1%
Febrile neutropenia	12	12	2%
2	1	1	0%
3	10	10	2%
4	1	1	0%
Platelet count decreased	2	2	0%
4	2	2	0%
Leukocytosis	1	1	0%
4	1	1	0%
Pancytopenia	1	1	0%
4	1	1	0%
Infections and infestations	**14**	**14**	**2%**
1	1	1	0%
2	2	2	0%
3	10	10	2%
4	1	1	0%
Thrush	2	2	0%
2	1	1	0%
3	1	1	0%
Lung infection	2	2	0%
3	2	2	0%
Upper respiratory infection	1	1	0%
1	1	1	0%
Infections and infestations - Other, specify	1	1	0%
2	1	1	0%
Enterocolitis infectious	1	1	0%
3	1	1	0%
Erysipelas	1	1	0%
3	1	1	0%
Gastroenteritis	1	1	0%
3	1	1	0%
Pseudomonas infection	1	1	0%
3	1	1	0%
Sepsis	1	1	0%
3	1	1	0%
Superinfection	1	1	0%
3	1	1	0%
Urinary tract infection	1	1	0%
3	1	1	0%
Encephalitis infection	1	1	0%
4	1	1	0%
Cardiac disorders	**12**	**10**	**2%**
1	1	1	0%
2	4	4	1%
3	6	4	1%
4	1	1	0%
Atrial fibrillation	10	8	1%
2	4	4	1%
3	6	4	1%
Paroxysmal atrial tachycardia	1	1	0%
1	1	1	0%
Myocardial infarction	1	1	0%
4	1	1	0%
Gastrointestinal disorders	**8**	**7**	**1%**
2	2	2	0%
3	5	4	1%
4	1	1	0%
Nausea	2	2	0%
2	1	1	0%
3	1	1	0%
Vomiting	2	2	0%
2	1	1	0%
3	1	1	0%
Diarrhea	2	2	0%
3	2	2	0%
Mucositis oral	1	1	0%
3	1	1	0%
Retroperitoneal haemorrhage	1	1	0%
4	1	1	0%
Metabolism and nutrition disorders	**3**	**3**	**1%**
2	1	1	0%
3	2	2	0%
Decreased appetite	2	2	0%
2	1	1	0%
3	1	1	0%
Tumour lysis syndrome	1	1	0%
3	1	1	0%

General disorders and administration site conditions	**3**	**3**	**1%**
2	1	1	0%
3	2	2	0%
Fever	2	2	0%
2	1	1	0%
3	1	1	0%
General disorders and administration site conditions - Other, specify	1	1	0%
3	1	1	0%
Renal and urinary disorders	**2**	**2**	**0%**
1	1	1	0%
4	1	1	0%
Haematuria	1	1	0%
1	1	1	0%
Acute kidney injury	1	1	0%
4	1	1	0%
Vascular disorders	**1**	**1**	**0%**
2	1	1	0%
Hematoma	1	1	0%
2	1	1	0%
Nervous system disorders	**1**	**1**	**0%**
3	1	1	0%
Haemorrhage intracranial	1	1	0%
3	1	1	0%
Respiratory, thoracic and mediastinal disorders	**1**	**1**	**0%**
3	1	1	0%
Pleural effusion	1	1	0%
3	1	1	0%
Skin and subcutaneous tissue disorders	**1**	**1**	**0%**
3	1	1	0%
Rash generalised	1	1	0%
3	1	1	0%
Investigations	**1**	**1**	**0%**
3	1	1	0%
White blood cell count increased	1	1	0%
3	1	1	0%

[1] SAE: serious adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table shows all SAEs related to Ibrutinib in the induction phase. The SAEs are shown according to SOC, PT and severity. No deaths occurred.

Table 6a shows all SAEs related to Ibrutinib in the induction phase. The SAEs are shown according to SOC, PT and severity. It can be observed that most SAEs are of grade 3. No deaths occurred in this phase which were related to Ibrutinib.

Table 6b: SAEs related to Ibrutinib in ASCT phase

SAEs [1] related to Ibrutinib by SOC [2], PT [3] and Grade	**Overall** events	(N = 254)	%
Blood and lymphatic system disorders	**2**	**2**	**1%**
4	2	2	1%
Bone marrow hypocellular	1	1	0%
4	1	1	0%
Pancytopenia	1	1	0%
4	1	1	0%
Gastrointestinal disorders	**1**	**1**	**0%**
3	1	1	0%
Gastrointestinal inflammation	1	1	0%
3	1	1	0%
Injury, poisoning and procedural complications	**1**	**1**	**0%**
3	1	1	0%
Transplant failure	1	1	0%
3	1	1	0%
Infections and infestations	**1**	**1**	**0%**
5	1	1	0%
Sepsis	1	1	0%
5	1	1	0%

[1] SAE: serious adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table shows all SAEs related to Ibrutinib in the ASCT phase. The SAEs are shown according to SOC, PT and severity. One death occurred because of Sepsis.

This table shows all SAEs related to Ibrutinib in the ASCT phase. The SAEs are shown according to SOC, PT and severity. Since no treatment with ibrutinib takes place in this phase, very few SAEs occur. However, there is one death due to Sepsis in this phase, which is related to Ibrutinib.

Table 6c: SAEs related to Ibrutinib in maintenance and follow-up phase

SAEs [1] related to Ibrutinib by SOC [2], PT [3] and Grade	**Overall** events	(N = 500)	%
Infections and infestations	**54**	**43**	**9%**
1	1	1	0%
2	7	7	1%
3	39	29	6%
4	7	6	1%
Lung infection	22	18	4%
2	4	4	1%
3	15	11	2%
4	3	3	1%
Shingles	7	7	1%
2	1	1	0%
3	6	6	1%
Sepsis	6	5	1%
3	2	2	0%
4	4	3	1%
Erysipelas	4	3	1%
2	1	1	0%
3	3	2	0%
Sinusitis	2	2	0%
3	2	2	0%
Upper respiratory infection	1	1	0%
1	1	1	0%
Groin abscess	1	1	0%
2	1	1	0%
Bronchial infection	1	1	0%
3	1	1	0%
Cranial nerve infection	1	1	0%
3	1	1	0%
Enterovirus infection	1	1	0%
3	1	1	0%
Escherichia infection	1	1	0%
3	1	1	0%
Lymph gland infection	1	1	0%
3	1	1	0%
Meningitis bacterial	1	1	0%
3	1	1	0%
Pharyngitis	1	1	0%
3	1	1	0%
Soft tissue infection	2	1	0%
3	2	1	0%
Staphylococcal infection	1	1	0%
3	1	1	0%
Varicella zoster virus infection	1	1	0%
3	1	1	0%
Blood and lymphatic system disorders	**22**	**21**	**4%**
3	13	12	2%
4	9	9	2%
Febrile neutropenia	13	12	2%
3	10	9	2%
4	3	3	1%
Neutrophil count decreased	6	6	1%
3	1	1	0%
4	5	5	1%
Platelet count decreased	2	2	0%
3	1	1	0%
4	1	1	0%
Pancytopenia	1	1	0%
3	1	1	0%
Cardiac disorders	**14**	**13**	**3%**
1	1	1	0%
2	2	2	0%
3	7	7	1%
4	4	3	1%
Atrial fibrillation	9	9	2%
1	1	1	0%
2	1	1	0%
3	6	6	1%
4	1	1	0%
Tachycardia	1	1	0%
2	1	1	0%
Pericarditis	1	1	0%
3	1	1	0%
Sinus bradycardia	1	1	0%
4	1	1	0%
Tachycardia induced cardiomyopathy	1	1	0%
4	1	1	0%
Ventricular fibrillation	1	1	0%

4	1	1	0%
Nervous system disorders	**9**	**8**	**2%**
2	5	4	1%
3	4	4	1%
Peripheral sensory neuropathy	4	3	1%
2	3	2	0%
3	1	1	0%
Transient ischaemic attack	1	1	0%
2	1	1	0%
VIIth nerve paralysis	1	1	0%
2	1	1	0%
Hemiparesis	1	1	0%
3	1	1	0%
Radiculopathy	1	1	0%
3	1	1	0%
Syncope	1	1	0%
3	1	1	0%
Respiratory, thoracic and mediastinal disorders	**4**	**4**	**1%**
1	1	1	0%
3	1	1	0%
4	2	2	0%
Interstitial lung disease	2	2	0%
3	1	1	0%
4	1	1	0%
Epistaxis	1	1	0%
1	1	1	0%
Pneumonitis	1	1	0%
4	1	1	0%
General disorders and administration site conditions	**5**	**4**	**1%**
1	3	2	0%
2	1	1	0%
3	1	1	0%
Fatigue	3	2	0%
1	3	2	0%
Fever	1	1	0%
2	1	1	0%
Inflammation	1	1	0%
3	1	1	0%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**4**	**4**	**1%**
2	1	1	0%
3	1	1	0%
4	1	1	0%
5	1	1	0%

Malignant melanoma	2	2	0%
3	1	1	0%
5	1	1	0%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) - Other, specify	1	1	0%
2	1	1	0%
Metastasis	1	1	0%
4	1	1	0%
Gastrointestinal disorders	**3**	**3**	**1%**
3	3	3	1%
Diarrhea	1	1	0%
3	1	1	0%
Gastroesophageal reflux disease	1	1	0%
3	1	1	0%
Gastrointestinal haemorrhage	1	1	0%
3	1	1	0%
Musculoskeletal and connective tissue disorders	**2**	**2**	**0%**
1	1	1	0%
3	1	1	0%
Arthralgia	1	1	0%
1	1	1	0%
Myositis	1	1	0%
3	1	1	0%
Vascular disorders	**2**	**2**	**0%**
3	2	2	0%
Hematoma	1	1	0%
3	1	1	0%
Hypotension	1	1	0%
3	1	1	0%
Immune system disorders	**1**	**1**	**0%**
1	1	1	0%
Hypersensitivity	1	1	0%
1	1	1	0%
Skin and subcutaneous tissue disorders	**1**	**1**	**0%**
1	1	1	0%
Skin haemorrhage	1	1	0%
1	1	1	0%
Investigations	**2**	**1**	**0%**
2	2	1	0%
Blood bilirubin increased	1	1	0%
2	1	1	0%
Creatinine increased	1	1	0%
2	1	1	0%
Metabolism and nutrition disorders	**1**	**1**	**0%**

3	1	1	0%	3	1	1	0%
Tumour lysis syndrome	1	1	0%				

[1] SAE: serious adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table shows all SAEs related to Ibrutinib in the maintenance phase. The SAEs are shown according to SOC, PT and severity. One death occurred because of Malignant melanoma.

This table shows all SAEs related to Ibrutinib in the maintenance and follow-up phase combined. The SAEs are shown according to SOC, PT and severity. In this phase, by far the most SAEs occurred in the SOC category Infections and infestations, with 54 events occurring in 43 patients, in which the PT Lung infection is the most often, with 22 events occurring in 18 patients. One death related to Ibrutinib occurred in this phase due to Malignant melanoma.

As can be seen in graphs 6a and 6b as well as in tables 6a to 6c, significantly fewer SAEs occur in the ASCT phases, as no treatment with Ibrutinib takes place. However, one death occurred in this phase, which is related to Ibrutinib. In addition, it should be noted that most SAEs come from the SOC categories Blood and lymphatic system disorders and Infections and infestations. Furthermore, it can be seen that most SAEs that occur are of grade 3.

In the following, the AEs according to different treatment groups will be explored. This is done with the help of tables 7a to 7c, which show all AEs that occur in a minimum of 2.5% of patients, again divided into the treatment phases.

Table 7a: Reclassified AEs in induction phase for treatment groups

AEs [1] by SOC [2] and PT [3]	**IR-CHOP/R-DHAP**			**R-CHOP/R-DHAP**			**Overall**		
	events	(N = 579)	%	events	(N = 287)	%	events	(N = 866)	%
Blood and lymphatic system disorders	**2548**	**465**	**80%**	**1153**	**217**	**76%**	**3701**	**682**	**79%**
Platelet count decreased	911	392	68%	397	180	63%	1308	572	66%
Neutrophil count decreased	742	309	53%	353	150	52%	1095	459	53%
Anemia	438	251	43%	214	126	44%	652	377	44%
White blood cell decreased	226	117	20%	98	54	19%	324	171	20%
Febrile neutropenia	89	74	13%	29	26	9%	118	100	12%
Lymphocyte count decreased	90	51	9%	48	24	8%	138	75	9%
Leukocytosis	28	26	4%	3	3	1%	31	29	3%
Gastrointestinal disorders	**996**	**340**	**59%**	**384**	**155**	**54%**	**1380**	**495**	**57%**
Nausea	306	177	31%	126	91	32%	432	268	31%
Constipation	113	93	16%	66	51	18%	179	144	17%
Diarrhea	152	105	18%	45	36	13%	197	141	16%
Vomiting	150	98	17%	51	38	13%	201	136	16%

Abdominal pain	58	48	8%	32	25	9%	90	73	8%
Dyspepsia	38	35	6%	12	11	4%	50	46	5%
Mucositis oral	42	35	6%	8	7	2%	50	42	5%
General disorders and administration site conditions	**534**	**269**	**46%**	**196**	**116**	**40%**	**730**	**385**	**44%**
Fatigue	185	133	23%	58	50	17%	243	183	21%
Fever	120	91	16%	61	48	17%	181	139	16%
Mucosal inflammation	51	40	7%	15	15	5%	66	55	6%
Generalized edema	33	22	4%	8	6	2%	41	28	3%
Pain	23	19	3%	6	6	2%	29	25	3%
Infections and infestations	**382**	**231**	**40%**	**121**	**85**	**30%**	**503**	**316**	**36%**
Infections and infestations - Other, specify	39	37	6%	17	16	6%	56	53	6%
Upper respiratory infection	27	25	4%	16	15	5%	43	40	5%
Urinary tract infection	24	20	3%	11	10	3%	35	30	3%
Lung infection	18	17	3%	9	9	3%	27	26	3%
Nervous system disorders	**368**	**223**	**39%**	**130**	**92**	**32%**	**498**	**315**	**36%**
Peripheral sensory neuropathy	127	107	18%	40	38	13%	167	145	17%
Headache	65	50	9%	26	21	7%	91	71	8%
Dysgeusia	45	40	7%	9	6	2%	54	46	5%
Paresthesia	35	33	6%	19	13	5%	54	46	5%
Dizziness	29	22	4%	10	10	3%	39	32	4%
Syncope	15	15	3%	11	9	3%	26	24	3%
Metabolism and nutrition disorders	**388**	**175**	**30%**	**130**	**71**	**25%**	**518**	**246**	**28%**
Hypokalemia	125	86	15%	34	28	10%	159	114	13%
Hypomagnesemia	55	41	7%	15	14	5%	70	55	6%
Hyperuricemia	34	28	5%	12	9	3%	46	37	4%
Hyperglycemia	34	28	5%	11	8	3%	45	36	4%
Decreased appetite	30	26	4%	12	10	3%	42	36	4%
Hypocalcemia	22	17	3%	6	6	2%	28	23	3%
Hyponatremia	16	13	2%	9	9	3%	25	22	3%
Investigations	**343**	**165**	**28%**	**153**	**76**	**26%**	**496**	**241**	**28%**
Creatinine increased	113	84	15%	64	36	13%	177	120	14%
GGT increased	37	27	5%	13	10	3%	50	37	4%
Alanine aminotransferase increased	34	23	4%	13	11	4%	47	34	4%
Weight gain	25	17	3%	10	7	2%	35	24	3%
Renal and urinary disorders	**158**	**127**	**22%**	**68**	**55**	**19%**	**226**	**182**	**21%**
Acute kidney injury	122	99	17%	54	43	15%	176	142	16%
Respiratory, thoracic and mediastinal disorders	**176**	**123**	**21%**	**56**	**41**	**14%**	**232**	**164**	**19%**
Cough	47	38	7%	8	8	3%	55	46	5%
Dyspnea	20	18	3%	19	13	5%	39	31	4%
Epistaxis	32	27	5%	5	4	1%	37	31	4%
Oropharyngeal pain	17	17	3%	6	6	2%	23	23	3%
Musculoskeletal and connective tissue disorders	**153**	**102**	**18%**	**56**	**48**	**17%**	**209**	**150**	**17%**
Back pain	42	36	6%	17	17	6%	59	53	6%

Bone pain	30	26	4%	21	18	6%	51	44	5%
Vascular disorders	**115**	**88**	**15%**	**53**	**46**	**16%**	**168**	**134**	**15%**
Hypertension	59	46	8%	19	17	6%	78	63	7%
Skin and subcutaneous tissue disorders	**143**	**107**	**18%**	**27**	**20**	**7%**	**170**	**127**	**15%**
Rash	37	32	6%	2	1	0%	39	33	4%
Injury, poisoning and procedural complications	**72**	**59**	**10%**	**40**	**29**	**10%**	**112**	**88**	**10%**
Infusion related reaction	53	43	7%	31	22	8%	84	65	8%
Ear and labyrinth disorders	**66**	**57**	**10%**	**29**	**25**	**9%**	**95**	**82**	**9%**
Tinnitus	27	26	4%	10	10	3%	37	36	4%
Hearing impaired	17	17	3%	9	9	3%	26	26	3%
Cardiac disorders	**75**	**59**	**10%**	**17**	**12**	**4%**	**92**	**71**	**8%**
Atrial fibrillation	31	25	4%	9	5	2%	40	30	3%
Psychiatric disorders	**43**	**34**	**6%**	**18**	**17**	**6%**	**61**	**51**	**6%**
Insomnia	16	14	2%	11	11	4%	27	25	3%
Immune system disorders	**28**	**26**	**4%**	**20**	**15**	**5%**	**48**	**41**	**5%**
Hypersensitivity	24	22	4%	14	12	4%	38	34	4%
Eye disorders	**21**	**20**	**3%**	**7**	**7**	**2%**	**28**	**27**	**3%**

[1] AE: adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table lists all AEs with their reclassified term according to SOC and PT in the induction phase that occur in a minimum of 2.5% of patients. This table is divided into two treatment groups and the overall group. The two treatment groups are IR-CHOP/R-DHAP, which means all patients who also received Ibrutinib in the induction phase, and R-CHOP/R-DHAP, which means all patients who did not receive Ibrutinib in the induction phase.

Table 7a lists all AEs with their reclassified term according to SOC and PT in the induction phase that occur in a minimum of 2.5% of patients. There are the two treatment groups IR-CHOP/R-DHAP, which means all patients who also received Ibrutinib in the induction phase, and R-CHOP/R-DHAP, which means all patients who did not receive Ibrutinib in the induction phase. In addition the overall values are displayed. For each treatment group, the number of AEs per event, the number of patients in whom this AE occurred at least once, and the percentage of patients are given. In this phase, five AEs after PT occur in at least 20% of patients in the three SOCs that occur in 40% of patients. In the SOC category Blood and lymphatic system disorders, these are the PTs Platelet count decreased, Neutrophil count decreased and Anemia. Furthermore, the PTs Nausea, in Gastrointestinal disorders, and Fatigue, in General disorders and administration site conditions, occur so frequently. It is striking that in some categories, clearly more AEs occur in the treatment group in which Ibrutinib was taken, which means that the difference is greater than 5%. This is the case in the following SOC categories General disorders and administration site conditions, Infections and infestations, Nervous

system disorders, Metabolism and nutrition disorders, Respiratory, thoracic and mediastinal disorders, Skin and subcutaneous tissue disorders and Cardiac disorders. On the other hand, it can be seen in the following PT categories Diarrhea, Fatigue, Peripheral sensory neuropath, Hypokalemia and Rash.

Table 7b: Reclassified AEs in ASCT phase for treatment groups

AEs [1] by SOC [2] and PT [3]	**IR-CHOP/R-DHAP**			**R-CHOP/R-DHAP**			**Overall**		
	events	(N = 254)	%	events	(N = 245)	%	events	(N = 499)	%
Blood and lymphatic system disorders	**495**	**167**	**66%**	**467**	**154**	**63%**	**962**	**321**	**64%**
Platelet count decreased	131	115	45%	146	120	49%	277	235	47%
Neutrophil count decreased	125	93	37%	119	91	37%	244	184	37%
Anemia	101	74	29%	76	66	27%	177	140	28%
Febrile neutropenia	71	69	27%	58	57	23%	129	126	25%
White blood cell decreased	49	43	17%	52	43	18%	101	86	17%
Lymphocyte count decreased	8	7	3%	10	9	4%	18	16	3%
General disorders and administration site conditions	**220**	**135**	**53%**	**185**	**128**	**52%**	**405**	**263**	**53%**
Mucosal inflammation	82	82	32%	71	71	29%	153	153	31%
Fever	79	67	26%	76	66	27%	155	133	27%
Fatigue	25	24	9%	15	14	6%	40	38	8%
Generalized edema	10	9	4%	7	7	3%	17	16	3%
Edema limbs	8	7	3%	6	6	2%	14	13	3%
Gastrointestinal disorders	**251**	**119**	**47%**	**252**	**122**	**50%**	**503**	**241**	**48%**
Diarrhea	55	51	20%	62	58	24%	117	109	22%
Nausea	55	47	19%	55	50	20%	110	97	19%
Mucositis oral	37	37	15%	41	40	16%	78	77	15%
Vomiting	22	18	7%	20	18	7%	42	36	7%
Abdominal pain	19	19	7%	16	15	6%	35	34	7%
Constipation	11	11	4%	11	10	4%	22	21	4%
Gastrointestinal inflammation	6	6	2%	9	9	4%	15	15	3%
Infections and infestations	**136**	**99**	**39%**	**125**	**93**	**38%**	**261**	**192**	**38%**
Infections and infestations - Other, specify	23	23	9%	14	12	5%	37	35	7%
Lung infection	22	21	8%	10	10	4%	32	31	6%
Sepsis	17	17	7%	8	8	3%	25	25	5%
Device related infection	10	10	4%	7	7	3%	17	17	3%
Metabolism and nutrition disorders	**94**	**57**	**22%**	**87**	**54**	**22%**	**181**	**111**	**22%**
Hypokalemia	36	34	13%	31	24	10%	67	58	12%
Decreased appetite	16	15	6%	17	17	7%	33	32	6%
Hypomagnesemia	11	11	4%	8	6	2%	19	17	3%
Skin and subcutaneous tissue disorders	**64**	**50**	**20%**	**40**	**34**	**14%**	**104**	**84**	**17%**
Rash	28	26	10%	17	14	6%	45	40	8%
Erythema	8	8	3%	5	5	2%	13	13	3%
Investigations	**54**	**35**	**14%**	**48**	**31**	**13%**	**102**	**66**	**13%**

GGT increased	9	8	3%	10	9	4%	19	17	3%
Alanine aminotransferase increased	8	8	3%	8	7	3%	16	15	3%
Respiratory, thoracic and mediastinal disorders	**44**	**35**	**14%**	**33**	**30**	**12%**	**77**	**65**	**13%**
Epistaxis	11	6	2%	8	8	3%	19	14	3%
Cough	6	6	2%	7	7	3%	13	13	3%
Nervous system disorders	**40**	**30**	**12%**	**31**	**27**	**11%**	**71**	**57**	**11%**
Headache	13	12	5%	10	10	4%	23	22	4%
Peripheral sensory neuropathy	14	12	5%	8	8	3%	22	20	4%
Vascular disorders	**31**	**28**	**11%**	**21**	**21**	**9%**	**52**	**49**	**10%**
Hypertension	10	9	4%	7	7	3%	17	16	3%
Cardiac disorders	**21**	**19**	**7%**	**17**	**15**	**6%**	**38**	**34**	**7%**
Musculoskeletal and connective tissue disorders	**13**	**11**	**4%**	**14**	**13**	**5%**	**27**	**24**	**5%**
Psychiatric disorders	**12**	**12**	**5%**	**9**	**9**	**4%**	**21**	**21**	**4%**
Renal and urinary disorders	**14**	**13**	**5%**	**7**	**6**	**2%**	**21**	**19**	**4%**
Injury, poisoning and procedural complications	**9**	**8**	**3%**	**9**	**8**	**3%**	**18**	**16**	**3%**

[1] AE: adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table lists all AEs with their reclassified term according to SOC and PT in the ASCT phase that occur in a minimum of 2.5% of patients. This table is divided into two treatment groups and the overall group. The two treatment groups are IR-CHOP/R-DHAP, which means all patients who also received Ibrutinib in the induction phase and started high dose treatment, and R-CHOP/R-DHAP, which means all patients who did not receive Ibrutinib in the induction phase and started high dose treatment.

Table 7b lists all AEs with their reclassified term according to SOC and PT in the ASCT phase that occur in a minimum of 2.5% of patients. There are the two treatment groups IR-CHOP/R-DHAP, which means all patients who also received Ibrutinib in the induction phase and started high dose treatment, and R-CHOP/R-DHAP, which means all patients who did not receive Ibrutinib in the induction phase and started high dose treatment. In addition the overall values are displayed. For each treatment group, the number of AEs per event, the number of patients in whom this AE occurred at least once, and the percentage of patients are given. In this phase, seven AEs after PT occur in at least 20% of patients in the three SOCs that occur in 40% of patients. In the SOC category Blood and lymphatic system disorders, these are the PTs Platelet count decreased, Neutrophil count decreased, Anemia and Febrile neutropenia. Furthermore, the PTs Mucosal inflammation and Fever, in General disorders and administration site conditions, and Diarrhea, occur quite frequently in the category Gastrointestinal disorders. In this phase, the differences in AEs between the treatment groups are smaller. However, more AEs occur in the IR-CHOP/R-DHAP treatment group but only in the SOC category Skin and subcutaneous tissue disorders the difference is again greater than 5%.

Table 7c: Reclassified AEs in maintenance and follow-up phase for treatment groups

AEs [1] by SOC [2] and PT [3]	**A**			**A + I**			**I**		
	events	(N = 238)	%	events	(N = 231)	%	events	(N = 269)	%
Infections and infestations	**147**	**80**	**34%**	**337**	**148**	**64%**	**294**	**137**	**51%**
Lung infection	22	19	8%	44	38	16%	45	33	12%
Corona virus infection	18	18	8%	30	26	11%	41	37	14%
Upper respiratory infection	16	13	5%	32	26	11%	24	22	8%
Shingles	17	14	6%	35	32	14%	7	7	3%
Infections and infestations - Other, specify	9	7	3%	21	20	9%	12	12	4%
Urinary tract infection	6	6	3%	12	8	3%	16	11	4%
Sinusitis	3	3	1%	11	10	4%	12	11	4%
Bronchial infection	6	5	2%	12	8	3%	9	7	3%
Blood and lymphatic system disorders	**126**	**64**	**27%**	**343**	**135**	**58%**	**186**	**95**	**35%**
Neutrophil count decreased	78	46	19%	220	109	47%	101	65	24%
Platelet count decreased	11	10	4%	43	32	14%	23	18	7%
Anemia	12	10	4%	21	18	8%	24	20	7%
White blood cell decreased	11	7	3%	31	21	9%	15	10	4%
Febrile neutropenia	6	6	3%	18	15	6%	6	6	2%
Gastrointestinal disorders	**39**	**30**	**13%**	**109**	**65**	**28%**	**114**	**69**	**26%**
Diarrhea	12	10	4%	45	35	15%	40	33	12%
Nausea	1	1	0%	7	7	3%	13	11	4%
General disorders and administration site conditions	**54**	**39**	**16%**	**77**	**50**	**22%**	**96**	**64**	**24%**
Fatigue	23	18	8%	29	23	10%	18	16	6%
Fever	16	13	5%	17	14	6%	29	27	10%
Musculoskeletal and connective tissue disorders	**23**	**20**	**8%**	**73**	**58**	**25%**	**94**	**56**	**21%**
Muscle cramp	2	2	1%	24	24	10%	27	21	8%
Myalgia	4	4	2%	20	19	8%	14	13	5%
Arthralgia	2	1	0%	8	7	3%	24	16	6%
Nervous system disorders	**30**	**28**	**12%**	**66**	**50**	**22%**	**74**	**55**	**20%**
Peripheral sensory neuropathy	14	14	6%	30	25	11%	22	21	8%
Paresthesia	4	4	2%	5	4	2%	14	11	4%
Skin and subcutaneous tissue disorders	**19**	**16**	**7%**	**88**	**58**	**25%**	**80**	**60**	**22%**
Rash	5	5	2%	19	17	7%	25	21	8%
Respiratory, thoracic and mediastinal disorders	**23**	**19**	**8%**	**67**	**48**	**21%**	**51**	**41**	**15%**
Cough	8	7	3%	32	27	12%	24	22	8%
Dyspnea	3	3	1%	11	10	4%	6	6	2%
Investigations	**19**	**16**	**7%**	**78**	**40**	**17%**	**31**	**20**	**7%**
Creatinine increased	8	6	3%	13	10	4%	8	7	3%
GGT increased	3	3	1%	20	14	6%	4	3	1%
Vascular disorders	**12**	**10**	**4%**	**20**	**16**	**7%**	**42**	**36**	**13%**
Hypertension	5	5	2%	1	1	0%	17	16	6%
Metabolism and nutrition disorders	**20**	**16**	**7%**	**26**	**23**	**10%**	**29**	**20**	**7%**

Cardiac disorders	**6**	**6**	**3%**	**20**	**17**	**7%**	**46**	**34**	**13%**
Atrial fibrillation	1	1	0%	10	9	4%	17	17	6%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**7**	**7**	**3%**	**13**	**13**	**6%**	**26**	**21**	**8%**
Injury, poisoning and procedural complications	**6**	**5**	**2%**	**10**	**9**	**4%**	**26**	**20**	**7%**
Renal and urinary disorders	**6**	**6**	**3%**	**10**	**8**	**3%**	**19**	**16**	**6%**
Psychiatric disorders	**8**	**5**	**2%**	**12**	**9**	**4%**	**17**	**14**	**5%**
Ear and labyrinth disorders	**8**	**8**	**3%**	**8**	**6**	**3%**	**16**	**14**	**5%**
Eye disorders	**6**	**6**	**3%**	**13**	**9**	**4%**	**9**	**9**	**3%**
Immune system disorders	**4**	**4**	**2%**	**11**	**11**	**5%**	**4**	**4**	**1%**

[1] AE: adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table lists all AEs with their reclassified term according to SOC and PT in the maintenance and follow-up phase that occur in a minimum of 2.5% of patients. This table is divided into the three treatment groups A, which means all patients who did not receive Ibrutinib in the induction phase, started high dose treatment and did not start Ibrutinib maintenance, A+I, which means all patients who received Ibrutinib in the induction phase and started high dose treatment and ibrutinib maintenance, and I, which means all patients who received Ibrutinib in the induction phase and Ibrutinib maintenance but did not start high dose treatment.

The table 7c lists all AEs with their reclassified term according to SOC and PT in the maintenance and follow-up phase that occur in a minimum of 2.5% of patients. There are the three treatment groups A, which means all patients who did not receive Ibrutinib in the induction phase, started high dose treatment and did not start Ibrutinib maintenance, A+I, which means all patients who received Ibrutinib in the induction phase, started high dose treatment and Ibrutinib maintenance, and I, which means all patients who received Ibrutinib in the induction phase, Ibrutinib maintenance but did not start high dose treatment. For each treatment group, the number of AEs per event, the number of patients in whom this AE occurred at least once, and the percentage of patients are given. In this phase, one AE after PT occur in at least 20% of patients, namely Neutrophil count decreased in Blood and lymphatic system disorders. In addition, there is one more SOC where AEs occur in at least 40% of patients, namely Infections and infestations. In this phase, clear differences can be seen between the treatment groups. The fewest AEs occurred in group A. For groups A+I and I, no clear statement can be made for AEs, but it can be said that more AEs occurred in group A+I than in group I.

All the points raised in this chapter should be included in the methods and results sections of a phase 3 clinical trial publication. Attention should still be paid to the study objectives.

As can be seen, a detailed analysis of the harms, as required by the extension of the CONSORT statement, is very time-consuming. In this chapter, it takes up to 17 pages. Since the benefits are also described in a publication and there is a limit to the length of a publication, it is almost impossible to fulfil all the criteria. Therefore, one should try to present all criteria briefly in the text of the publication. However, some criteria cannot be presented completely in the body of the publication, such as criteria 13) or 14). These criteria were not completely fulfilled in this thesis either. A cut-off was used and not all AEs were presented according to severity. These criteria should then, if it is not possible to fulfil them in the text, either through graphs, tables or in the main body, be presented in the Supplemental Material. This way, it is possible to meet all the criteria, but in addition to use the limited space available. Another way to react to this problem is to consider different criteria together. However, this is only possible in the results section, as there is no possibility for this in the methods. The criteria that can be displayed together are criteria 12), states whether in addition also the absolute number of AEs is reported, 13), states whether AEs are not only reported above a certain frequency cut-off, and 14), states whether AEs of different severity grades are reported but not combined in severity grades. They can be presented both graphically and in tabular form, although criterion 13) is often not so easy to fulfil in the case of graphs.

4.2.2 Differences between reported and reclassified AE definitions

In this chapter, the differences in the results for AEs are observed. The main focus is on the differences between the reported, after MedDRA definition, and reclassified, after CTCAE definition, representation of AEs in data. First of all, these differences are highlighted by using the number of absolute events occurring.

To begin with, the differences in the number of events per SOC categories are considered. These are shown in Table 8 and will now be examined in more detail.

Table 8: Differences between reported and reclassified SOC terms

AE [1] by SOC [2]	**N reclassified**	**N reported**	**Difference**
Investigations	730	2585	1855
Blood and lymphatic system disorders	5361	3526	-1835
Metabolism and nutrition disorders	780	764	-16
Gastrointestinal disorders	2162	2158	-4
Vascular disorders	295	291	-4
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	56	52	-4
Reproductive system and breast disorders	24	27	3
Congenital, familial and genetic disorders	4	7	3
NA	3	0	-3
General disorders and administration site conditions	1374	1372	-2
Infections and infestations	1579	1580	1
Nervous system disorders	747	748	1
Cardiac disorders	207	208	1
Injury, poisoning and procedural complications	176	177	1
Ear and labyrinth disorders	136	135	-1
Product issues	0	1	1
Skin and subcutaneous tissue disorders	463	463	0
Respiratory, thoracic and mediastinal disorders	463	463	0
Musculoskeletal and connective tissue disorders	437	437	0
Renal and urinary disorders	285	285	0
Psychiatric disorders	122	122	0
Immune system disorders	77	77	0
Eye disorders	65	65	0
Hepatobiliary disorders	32	32	0
Endocrine disorders	8	8	0
Surgical and medical procedures	2	2	0
Social circumstances	1	1	0

[1] AE: adverse event; [2] SOC: system organ class

This table shows the differences between the reported and reclassified SOC categories. The absolute numbers for both categories, reclassified and reported SOCs, are given, as well as the difference between reported and reclassified AEs. The largest differences are in the SOC terms Blood and lymphatic disorders and Investigations.

Table 8 shows the differences between the numbers of reported and reclassified AEs by SOC. The absolute values for the reported and reclassified AEs are shown, as well as the difference between reported and reclassified AEs. It can be observed that there were major changes in two categories in particular. After reclassification, there are significantly fewer investigations, while there are significantly more blood and lymphatic system disorders. In all other SOC terms, the differences are only very slight and are not particularly noticeable.

In addition to the differences in the SOCs, there are also some differences in the PTs, which are examined in more detail below with Table 9.

Table 9: Differences between reported and reclassified PT terms

AEs [1] by PT [2]	**N reclassified**	**N reported**	**Difference**
Neutrophil count decreased	1753	617	-1136
Neutropenia	0	1115	1115
Anemia	896	0	-896
Anaemia	0	886	886
Thrombocytopenia	0	884	884
Platelet count decreased	1669	785	-884
White blood cell decreased	483	0	-483
Diarrhea	416	0	-416
Diarrhoea	0	415	415
Fever	400	0	-400
Pyrexia	0	398	398
White blood cell count decreased	0	268	268
Hypokalemia	244	0	-244
Hypokalaemia	0	230	230
Creatinine increased	216	0	-216
Leukopenia	0	215	215
Blood creatinine increased	0	214	214
Acute kidney injury	201	28	-173
Peripheral sensory neuropathy	257	85	-172
Lung infection	176	22	-154
Mucositis oral	145	0	-145
Fatigue	356	214	-142
Asthenia	0	142	142
Infections and infestations - Other, specify	135	0	-135
Stomatitis	0	133	133
Pneumonia	0	131	131
Upper respiratory infection	131	0	-131
Gamma-glutamyltransferase increased	0	96	96
GGT increased	96	0	-96
Renal failure acute	0	94	94

Hypomagnesemia	93	0	-93
Hypomagnesaemia	0	92	92
Polyneuropathy	0	90	90
Neuropathy peripheral	0	82	82
Upper respiratory tract infection	0	82	82
Paraesthesia	0	80	80
Paresthesia	80	0	-80
Dyspnea	72	0	-72
Muscle spasms	0	70	70
Muscle cramp	70	0	-70
Oedema	0	68	68
Generalized edema	68	0	-68
Dyspnoea	0	67	67
Infection	0	66	66
Shingles	66	0	-66
Abdominal pain	151	86	-65
Herpes zoster	0	65	65
Hyperuricaemia	0	64	64
Hyperuricemia	64	0	-64
Abdominal pain upper	0	62	62
Renal failure	0	61	61
Hyperglycaemia	0	56	56
Hyperglycemia	56	0	-56
Bronchial infection	50	0	-50

[1] AE: adverse event; [2] PT: preferred term

This table shows the differences between the reported and reclassified PTs. The absolute numbers for both categories are given, as well as the difference between reported and reclassified AEs. There are only PTs given with a difference between reported and reclassified greater than 50. There are many PTs with large differences given in the table.

Table 9 shows the differences between reported and reclassified AEs by PT. The absolute values for the reported and reclassified AEs are shown, as well as the differences between reported and reclassified AEs. First of all, it can be seen that in contrast to the SOCs, large differences can be seen in significantly more PTs. In the table, only those PTs are shown in which the difference is greater than 50, which is a total of 54 PTs. In total, there are 319 PTs in which the number of AEs differs between reported and reclassified. In the following six terms alone, the difference is greater than 800: Neutrophil count decreased, Neutropenia, Anemia, Anaemia, Thrombocytopenia and Platelet count decreased. Most of the differences are given for AEs not occurring before reclassification, or for AEs disappearing after reclassification. This is, because many AEs, which have big differences, occur because of the different spellings. Examples include

Anaemia or Anamia, White blood cell count decreased or White blood cell decreased or Blood creatinine increased or Creatinine increased. A total of 209 PTs reported are no longer present after reclassification, while 73 previously non-existent PTs are now part of the occurring AEs. Furthermore, only in 36 PTs the number of occurring AEs has changed due to the reclassification. These terms are the ones that are particularly interesting, as a direct shift in PTs could be seen here. One example is, the combination of the two PTs Thrombocytopenia and Platelet count decreased into PT Platelet count decreased.

Overall, it can be seen that some PTs have been combined as a result of the reclassification. One example is that the term White blood cell decreased is the combination of the terms White blood cell count decreased and Leukopenia. However, many PTs have not been reclassified because they have not occurred at least ten times. Therefore, some AEs are probably still in the reclassification according to MedDRA definition and not according to CTCAE definition, as it should be. This point should always be kept in mind when evaluating the AEs in the study.

Now it is compared how the number of AEs has changed from reported to reclassified terms. Therefore, tables 7a to 7c are compared with the now following tables 10a to 10c.

Table 10a: Reported AEs in induction phase for treatment groups

AEs [1] by SOC [2] and PT [3]	**IR-CHOP/R-DHAP**			**R-CHOP/R-DHAP**			**Overall**		
	events	(N = 579)	%	events	(N = 287)	%	events	(N = 866)	%
Blood and lymphatic system disorders	**1668**	**415**	**72%**	**750**	**187**	**65%**	**2418**	**602**	**70%**
Anaemia	431	248	43%	213	125	44%	644	373	43%
Thrombocytopenia	481	223	39%	218	102	36%	699	325	38%
Neutropenia	476	191	33%	220	94	33%	696	285	33%
Febrile neutropenia	89	74	13%	29	26	9%	118	100	12%
Leukopenia	111	60	10%	50	29	10%	161	89	10%
Leukocytosis	28	26	4%	3	3	1%	31	29	3%
Gastrointestinal disorders	**994**	**339**	**59%**	**384**	**155**	**54%**	**1378**	**494**	**57%**
Nausea	306	177	31%	126	91	32%	432	268	31%
Constipation	113	93	16%	66	51	18%	179	144	17%
Diarrhoea	151	104	18%	45	36	13%	196	140	16%
Vomiting	150	98	17%	51	38	13%	201	136	16%
Dyspepsia	38	35	6%	12	11	4%	50	46	5%
Abdominal pain	31	27	5%	17	15	5%	48	42	5%
Stomatitis	37	33	6%	8	7	2%	45	40	5%
Abdominal pain upper	26	23	4%	14	12	4%	40	35	4%
Investigations	**1239**	**322**	**56%**	**558**	**142**	**49%**	**1797**	**464**	**54%**

Platelet count decreased	430	188	32%	179	84	29%	609	272	31%
Neutrophil count decreased	256	123	21%	131	58	20%	387	181	21%
Blood creatinine increased	113	84	15%	63	35	12%	176	119	14%
White blood cell count decreased	115	62	11%	48	25	9%	163	87	10%
Lymphocyte count decreased	69	36	6%	44	20	7%	113	56	6%
Gamma-glutamyltransferase increased	37	27	5%	13	10	3%	50	37	4%
Alanine aminotransferase increased	34	23	4%	13	11	4%	47	34	4%
Weight increased	25	17	3%	10	7	2%	35	24	3%
General disorders and administration site conditions	**533**	**269**	**46%**	**196**	**115**	**40%**	**729**	**384**	**44%**
Pyrexia	120	91	16%	61	48	17%	181	139	16%
Fatigue	116	87	15%	29	26	9%	145	113	13%
Asthenia	69	48	8%	29	25	9%	98	73	8%
Mucosal inflammation	51	40	7%	15	15	5%	66	55	6%
Oedema	33	22	4%	8	6	2%	41	28	3%
Pain	23	19	3%	6	6	2%	29	25	3%
Infections and infestations	**384**	**233**	**40%**	**121**	**85**	**30%**	**505**	**318**	**37%**
Urinary tract infection	23	19	3%	11	10	3%	34	29	3%
Infection	18	17	3%	12	12	4%	30	29	3%
Nervous system disorders	**369**	**224**	**39%**	**130**	**92**	**32%**	**499**	**316**	**36%**
Headache	65	50	9%	26	21	7%	91	71	8%
Neuropathy peripheral	40	36	6%	15	14	5%	55	50	6%
Peripheral sensory neuropathy	45	35	6%	15	14	5%	60	49	6%
Polyneuropathy	42	39	7%	10	10	3%	52	49	6%
Paraesthesia	35	33	6%	19	13	5%	54	46	5%
Dysgeusia	44	39	7%	9	6	2%	53	45	5%
Dizziness	29	22	4%	10	10	3%	39	32	4%
Syncope	15	15	3%	11	9	3%	26	24	3%
Metabolism and nutrition disorders	**376**	**170**	**29%**	**128**	**69**	**24%**	**504**	**239**	**28%**
Hypokalaemia	114	81	14%	33	27	9%	147	108	12%
Hypomagnesaemia	55	41	7%	14	13	5%	69	54	6%
Hyperuricaemia	34	28	5%	12	9	3%	46	37	4%
Hyperglycaemia	34	28	5%	11	8	3%	45	36	4%
Decreased appetite	30	26	4%	12	10	3%	42	36	4%
Hypocalcaemia	22	17	3%	6	6	2%	28	23	3%
Hyponatraemia	16	13	2%	9	9	3%	25	22	3%
Renal and urinary disorders	**158**	**127**	**22%**	**68**	**55**	**19%**	**226**	**182**	**21%**
Renal failure acute	56	48	8%	31	24	8%	87	72	8%
Renal failure	37	30	5%	14	13	5%	51	43	5%
Respiratory, thoracic and mediastinal disorders	**176**	**123**	**21%**	**56**	**41**	**14%**	**232**	**164**	**19%**
Cough	47	38	7%	8	8	3%	55	46	5%
Dyspnoea	20	18	3%	19	13	5%	39	31	4%
Epistaxis	32	27	5%	5	4	1%	37	31	4%
Oropharyngeal pain	17	17	3%	6	6	2%	23	23	3%

Musculoskeletal and connective tissue disorders	**153**	**102**	**18%**	**56**	**48**	**17%**	**209**	**150**	**17%**
Back pain	42	36	6%	17	17	6%	59	53	6%
Bone pain	30	26	4%	21	18	6%	51	44	5%
Vascular disorders	**111**	**86**	**15%**	**52**	**46**	**16%**	**163**	**132**	**15%**
Hypertension	52	43	7%	17	15	5%	69	58	7%
Skin and subcutaneous tissue disorders	**142**	**107**	**18%**	**27**	**20**	**7%**	**169**	**127**	**15%**
Rash	37	32	6%	2	1	0%	39	33	4%
Injury, poisoning and procedural complications	**74**	**60**	**10%**	**40**	**29**	**10%**	**114**	**89**	**10%**
Infusion related reaction	53	43	7%	31	22	8%	84	65	8%
Ear and labyrinth disorders	**65**	**56**	**10%**	**29**	**25**	**9%**	**94**	**81**	**9%**
Tinnitus	27	26	4%	10	10	3%	37	36	4%
Cardiac disorders	**75**	**59**	**10%**	**18**	**13**	**5%**	**93**	**72**	**8%**
Atrial fibrillation	31	25	4%	9	5	2%	40	30	3%
Psychiatric disorders	**43**	**34**	**6%**	**18**	**17**	**6%**	**61**	**51**	**6%**
Insomnia	16	14	2%	11	11	4%	27	25	3%
Immune system disorders	**28**	**26**	**4%**	**20**	**15**	**5%**	**48**	**41**	**5%**
Hypersensitivity	24	22	4%	14	12	4%	38	34	4%
Eye disorders	**21**	**20**	**3%**	**7**	**7**	**2%**	**28**	**27**	**3%**

[1] AE: adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table lists all AEs with their reported term according to SOC and PT in the induction phase that occur in a minimum of 2.5% of patients. This table is divided into two treatment groups and the overall group. The two treatment groups are IR-CHOP/R-DHAP, which means all patients who received Ibrutinib in the induction phase, and R-CHOP/R-DHAP, which means all patients who did not receive Ibrutinib in the induction phase.

Table 10a lists all AEs with their reported term according to SOC and PT in the induction phase that occur in a minimum of 2.5% of patients. A brief comparison is now made between this table and table 7a. It is particularly noticeable that the SOC term Investigations occurs significantly more frequently than in the reclassified data. The second SOC term for which a change can be seen is Blood and lymphatic system disorders, which occurs significantly less frequently. Differences in frequency can also be seen for some PTs. Some PTs are grouped together. As an example, the PTs Abdominal pain and Abdominal upper pain, which occur here, are combined into the reclassified PT Abdominal pain. The change in PTs in the SOC category Infections and infestations is particularly striking. Examples of this are the PTs Upper respiratory infection and Lung infection, which occur less frequently before reclassification. Furthermore, the reclassification also results in fewer PTs overall, which occur more frequently. It should also be mentioned that some PTs are now assigned to other SOCs as a result of the reclassification. An example of this is the PT Neutrophil count decreased, which after reclassifica-

tion no longer belongs to Investigations but to Blood and lymphatic system disorders. This is combined with the PT Neutropenia.

In the following, the AEs in the ASCT phase are compared. Tables 7b and the following table 10b are used for this purpose.

Table 10b: Reported AEs in ASCT phase for treatment groups

AEs [1] by SOC [2] and PT [3]	**IR-CHOP/R-DHAP**			**R-CHOP/R-DHAP**			**Overall**		
	events	(N = 254)	%	events	(N = 245)	%	events	(N = 499)	%
Blood and lymphatic system disorders	**323**	**148**	**58%**	**303**	**139**	**57%**	**626**	**287**	**58%**
Anaemia	101	74	29%	75	65	27%	176	139	28%
Febrile neutropenia	71	69	27%	58	57	23%	129	126	25%
Thrombocytopenia	59	56	22%	73	65	27%	132	121	24%
Neutropenia	65	52	20%	71	51	21%	136	103	21%
Leukopenia	17	16	6%	20	18	7%	37	34	7%
General disorders and administration site conditions	**220**	**135**	**53%**	**185**	**128**	**52%**	**405**	**263**	**53%**
Mucosal inflammation	82	82	32%	71	71	29%	153	153	31%
Pyrexia	79	67	26%	75	65	27%	154	132	26%
Fatigue	17	16	6%	8	8	3%	25	24	5%
Oedema	10	9	4%	7	7	3%	17	16	3%
Asthenia	8	8	3%	7	6	2%	15	14	3%
Oedema peripheral	8	7	3%	6	6	2%	14	13	3%
Gastrointestinal disorders	**251**	**119**	**47%**	**252**	**122**	**50%**	**503**	**241**	**48%**
Diarrhoea	55	51	20%	62	58	24%	117	109	22%
Nausea	55	47	19%	55	50	20%	110	97	19%
Stomatitis	37	37	15%	40	40	16%	77	77	15%
Vomiting	22	18	7%	20	18	7%	42	36	7%
Abdominal pain	13	13	5%	10	9	4%	23	22	4%
Constipation	11	11	4%	11	10	4%	22	21	4%
Gastrointestinal inflammation	6	6	2%	9	9	4%	15	15	3%
Infections and infestations	**136**	**99**	**39%**	**125**	**93**	**38%**	**261**	**192**	**38%**
Pneumonia	16	15	6%	6	6	2%	22	21	4%
Infection	15	15	6%	5	4	2%	20	19	4%
Device related infection	10	10	4%	7	7	3%	17	17	3%
Sepsis	10	10	4%	5	5	2%	15	15	3%
Investigations	**225**	**89**	**35%**	**212**	**86**	**35%**	**437**	**175**	**35%**
Platelet count decreased	72	60	24%	73	55	22%	145	115	23%
Neutrophil count decreased	58	39	15%	47	39	16%	105	78	16%
White blood cell count decreased	32	28	11%	32	25	10%	64	53	11%
Gamma-glutamyltransferase increased	9	8	3%	10	9	4%	19	17	3%
Lymphocyte count decreased	8	7	3%	9	8	3%	17	15	3%
Alanine aminotransferase increased	8	8	3%	8	7	3%	16	15	3%
Metabolism and nutrition disorders	**94**	**57**	**22%**	**87**	**54**	**22%**	**181**	**111**	**22%**

Hypokalaemia	36	34	13%	31	24	10%	67	58	12%
Decreased appetite	16	15	6%	17	17	7%	33	32	6%
Hypomagnesaemia	11	11	4%	8	6	2%	19	17	3%
Skin and subcutaneous tissue disorders	**64**	**50**	**20%**	**40**	**34**	**14%**	**104**	**84**	**17%**
Rash	28	26	10%	17	14	6%	45	40	8%
Erythema	8	8	3%	5	5	2%	13	13	3%
Respiratory, thoracic and mediastinal disorders	**44**	**35**	**14%**	**33**	**30**	**12%**	**77**	**65**	**13%**
Epistaxis	11	6	2%	8	8	3%	19	14	3%
Cough	6	6	2%	7	7	3%	13	13	3%
Nervous system disorders	**40**	**30**	**12%**	**31**	**27**	**11%**	**71**	**57**	**11%**
Headache	13	12	5%	10	10	4%	23	22	4%
Vascular disorders	**31**	**28**	**11%**	**22**	**22**	**9%**	**53**	**50**	**10%**
Hypertension	8	7	3%	7	7	3%	15	14	3%
Cardiac disorders	**21**	**19**	**7%**	**17**	**15**	**6%**	**38**	**34**	**7%**
Musculoskeletal and connective tissue disorders	**13**	**11**	**4%**	**14**	**13**	**5%**	**27**	**24**	**5%**
Psychiatric disorders	**12**	**12**	**5%**	**9**	**9**	**4%**	**21**	**21**	**4%**
Renal and urinary disorders	**14**	**13**	**5%**	**7**	**6**	**2%**	**21**	**19**	**4%**
Injury, poisoning and procedural complications	**9**	**8**	**3%**	**7**	**6**	**2%**	**16**	**14**	**3%**

[1] AE: adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table lists all AEs according to SOC and PT in the ASCT phase that occur in a minimum of 2.5% of patients. This table is divided into two treatment groups and the overall group. The two treatment groups are IR-CHOP/R-DHAP, which means all patients who received Ibrutinib in the induction phase and started high dose treatment, and R-CHOP/R-DHAP, which means all patients who did not receive Ibrutinib in the induction phase and started high dose treatment.

Table 10b lists all AEs with their reported term according to SOC and PT in the ASCT phase that occur in a minimum of 2.5% of patients. A brief comparison is now made between this table and table 7b. Almost all observations that already occurred in the comparison of AEs in the induction phase occurred again. The same changes can be seen for the two SOCs Blood and lymphatic system disorders and Investigations. For the more frequently occurring PTs that can be seen in this table, there are also no clear differences to the findings already obtained from the comparison in the induction phase. Otherwise, there are no new anomalies in this table that should be considered additionally. As a last point the AEs in the maintenance and follow-up phase are compared. Tables 7c and the following table 10c are used for this purpose. Only newly emerging differences that cannot be identified from the previous comparisons will be addressed here.

Table 10c: Reported AEs in maintenance and follow-up phase for treatment groups

AEs [1] by SOC [2] and PT [3]	A			A + I			I		
	events	(N = 238)	%	events	(N = 231)	%	events	(N = 269)	%
Infections and infestations	**147**	**80**	**34%**	**336**	**147**	**64%**	**294**	**137**	**51%**
Corona virus infection	18	18	8%	30	26	11%	41	37	14%
Pneumonia	19	17	7%	33	28	12%	34	26	10%
Herpes zoster	16	13	5%	35	32	14%	7	7	3%
Upper respiratory tract infection	11	8	3%	26	21	9%	12	12	4%
Urinary tract infection	6	6	3%	12	8	3%	16	11	4%
Sinusitis	3	3	1%	11	10	4%	12	11	4%
Nasopharyngitis	5	5	2%	6	6	3%	12	10	4%
Bronchitis	6	5	2%	12	8	3%	8	6	2%
Blood and lymphatic system disorders	**88**	**51**	**21%**	**238**	**113**	**49%**	**119**	**70**	**26%**
Neutropenia	57	32	13%	151	86	37%	62	42	16%
Anaemia	12	10	4%	20	18	8%	24	20	7%
Thrombocytopenia	8	7	3%	29	20	9%	13	9	3%
Febrile neutropenia	6	6	3%	18	15	6%	6	6	2%
Gastrointestinal disorders	**39**	**30**	**13%**	**109**	**65**	**28%**	**112**	**68**	**25%**
Diarrhoea	12	10	4%	45	35	15%	40	33	12%
Nausea	1	1	0%	7	7	3%	13	11	4%
Investigations	**56**	**32**	**13%**	**184**	**73**	**32%**	**101**	**53**	**20%**
Neutrophil count decreased	20	15	6%	64	31	13%	39	26	10%
White blood cell count decreased	10	6	3%	21	13	6%	10	6	2%
Platelet count decreased	3	3	1%	14	12	5%	10	9	3%
Blood creatinine increased	8	6	3%	13	10	4%	7	6	2%
Gamma-glutamyltransferase increased	3	3	1%	20	14	6%	4	3	1%
General disorders and administration site conditions	**54**	**39**	**16%**	**78**	**50**	**22%**	**96**	**64**	**24%**
Pyrexia	16	13	5%	16	13	6%	29	27	10%
Fatigue	11	10	4%	16	13	6%	14	12	4%
Asthenia	12	10	4%	13	11	5%	4	4	1%
Musculoskeletal and connective tissue disorders	**23**	**20**	**8%**	**73**	**58**	**25%**	**94**	**56**	**21%**
Muscle spasms	2	2	1%	24	24	10%	27	21	8%
Myalgia	2	2	1%	15	14	6%	10	10	4%
Arthralgia	2	1	0%	8	7	3%	24	16	6%
Nervous system disorders	**30**	**28**	**12%**	**66**	**50**	**22%**	**74**	**55**	**20%**
Polyneuropathy	9	9	4%	11	10	4%	6	6	2%
Neuropathy peripheral	3	3	1%	11	11	5%	8	7	3%
Paraesthesia	4	4	2%	5	4	2%	14	11	4%
Skin and subcutaneous tissue disorders	**19**	**16**	**7%**	**88**	**58**	**25%**	**82**	**61**	**23%**
Rash	5	5	2%	19	17	7%	25	21	8%
Respiratory, thoracic and mediastinal disorders	**23**	**19**	**8%**	**67**	**48**	**21%**	**51**	**41**	**15%**
Cough	8	7	3%	32	27	12%	24	22	8%
Vascular disorders	**12**	**10**	**4%**	**20**	**16**	**7%**	**42**	**36**	**13%**

Hypertension	5	5	2%	1	1	0%	17	16	6%
Cardiac disorders	**6**	**6**	**3%**	**20**	**17**	**7%**	**46**	**34**	**13%**
Atrial fibrillation	1	1	0%	10	9	4%	17	17	6%
Metabolism and nutrition disorders	**20**	**16**	**7%**	**25**	**22**	**10%**	**28**	**19**	**7%**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**7**	**7**	**3%**	**13**	**13**	**6%**	**23**	**18**	**7%**
Injury, poisoning and procedural complications	**6**	**5**	**2%**	**11**	**10**	**4%**	**26**	**20**	**7%**
Renal and urinary disorders	**6**	**6**	**3%**	**10**	**8**	**3%**	**19**	**16**	**6%**
Psychiatric disorders	**8**	**5**	**2%**	**12**	**9**	**4%**	**17**	**14**	**5%**
Ear and labyrinth disorders	**8**	**8**	**3%**	**8**	**6**	**3%**	**16**	**14**	**5%**
Eye disorders	**6**	**6**	**3%**	**13**	**9**	**4%**	**9**	**9**	**3%**
Immune system disorders	**4**	**4**	**2%**	**11**	**11**	**5%**	**4**	**4**	**1%**

[1] AE: adverse event; [2] SOC: system organ class; [3] PT: preferred term

This table lists all AEs according to SOC and PT in the maintenance and follow-up phase that occur in a minimum of 2.5% of patients. This table is divided into the three treatment groups A, which means all patients who did not receive Ibrutinib in the induction phase, started high dose treatment and did not start Ibrutinib maintenance, A+I, which means all patients who received Ibrutinib in the induction phase, started high dose treatment and Ibrutinib maintenance, and I, which means all patients who received Ibrutinib in the induction phase and Ibrutinib maintenance but did not start high dose treatment.

Table 10c lists all AEs with their reported term according to SOC and PT in the maintenance and follow-up phase that occur in a minimum of 2.5% of patients. In doing so, no new insights can be gained from comparing tables 7c and 10c to those already achieved.

It can be seen in all phases that some PTs have been grouped together and therefore it can be assumed that in the coding according to MedDRA a potential underreporting of some harms take place. This can be prevented by reclassifying according to CTCAE, as fewer PTs occur there. For this reason, it made sense to carry out the reclassification, but one would also have to reclassify the remaining PTs in order to be able to make a definitive statement.

In addition, as result of the analysis of differences between reported and reclassified terms for SOCs and PTs, it can be said that there are some clear differences in the classification of AEs. These are partly due to the reclassification, in which the same side effects are given different terms by different PT definitions, although the number of AEs occurring does not change. However, for some AEs, it can also be observed that they occur clearly more frequently or less frequently after reclassification.

5. Discussion

Now that the various analyses have been carried out, this chapter concludes by summarising the results and critically examining the methods used.

In the thesis, the presentation of AEs in publications of clinical phase 3 studies was examined. At the beginning, various suggestions were reported on how the presentation should be carried out. Subsequently, papers from the two journals The Lancet and NEJM were examined to see how well the suggestions were already implemented in the publications. Finally, using data from the TRIANGLE trial, an attempt was made to find the best possible representation of AEs for a publication, whereby differences in different AE definitions were shown.

First, the most striking results from chapters 2 to 4 are elaborated and presented across chapters. In the analysis of the papers, it is particularly noticeable that criteria that dealt purely with naming a definition performed significantly better than criteria that dealt with justifying a certain decision. This resulted in very large differences in the fulfilment of individual criteria by the publications analysed. Another striking point was that papers from The Lancet performed better than papers from the NEJM. In addition, it could be seen that the differences were concentrated on some criteria and were not evenly distributed across the criteria. The differences between the papers from oncology and the other medical fields are very small overall. However, there are also some criteria that were taken into account clearly better by one category. For example the criteria 6), states whether articles specifies early stopping rule, and 11), states whether AEs are also represented via graphs, are reported better by oncology papers, while criterion 2), states whether benefits and harms are addressed in introduction, for example, is reported better by papers from other medical fields. Although some criteria are already taken into account well to very well, for example the criteria 13), states whether AEs are not only reported above a certain frequency cut-off, and 14 ii), states whether AEs of different severity are not reported combined, it must be said in conclusion that all papers still have potential for improvement in the presentation of AEs. In the analysis carried out in chapter 4.2.1, which tried to give as good an example as possible of how all the criteria are taken into account, the following is particularly noticeable: If one wants to consider all points, this is not possible in the main body of the publication due to the limited number of characters, tables and graphics, as there is not enough room to include every-

thing. Therefore, use should always be made of supplemental material in publications where additional tables and graphics can be seen. Furthermore, it has been shown that different definitions used can lead to different results in the evaluation, simply because the frequencies of the occurring AE terms change, as can be seen in chapter 4.2.2. Here, too, the decision on which definitions to use is usually made in advance, but this decision is usually not explained. Nevertheless, clear differences are discernible only for very few PTs, but these are the important ones. Furthermore, a comparison was made between the reported and reclassified terms, in which some differences were found that suggest a possible underreporting of harms by the MedDRA coding in the reported terms. This is particularly noticeable in the PTs of the SOC category Infections and infestations. Another point that stood out is the large increase in AEs in SOC term Blood and lymphatic system disorders, which is accompanied by a clear decrease in AEs in SOC term Investigations.

However, it is not possible to make general statements from the points presented in this paper. This is mainly due to some limitations that had to be made or problems that arose. It should be noted that the focus was only on very specific proposals for the presentation of AEs. In this paper, only the proposals of the CONSORT group with an extension, as well as the specifications of the journals were considered for clinical phase 3 studies. These are only proposals that relate directly to the presentation of harms in the publication. However, there is already a choice of possibilities when AEs are recorded in studies. Definitions that are already set differently there can later lead to different results in the publications. These possibilities, which are addressed in the ICH guidelines, among others, were not considered here. Therefore, ICH guidelines and CONSORT extension statements should both be taken into account and compared during the preparation of the study. There are also a few points in the results in Chapter 3 that must be viewed critically. Firstly, with 33 articles, only a very small number of papers were examined. Furthermore, the difference in the number of articles in the categories examined, i.e. according to journals and medical field, is relatively large at five articles each due to the low total number. In addition, it should be mentioned that the study periods for the two journals differ and discrepancies may have occurred due to this. In chapter 4, an analysis with AE data was then carried out based on the previous results. In addition to the limitations already mentioned for a generalisation from chapters 2 and 3, further limitations must be taken into account. At the beginning the manual reclassification was only carried out on the PTs. The SOCs were not reclassified at first, but only

afterwards via hard coding for the PTs occurring in more than one SOC category. In addition, only those PTs were reclassified that occurred at least ten times. However, a PT could still be in the wrong SOC category without this having been noticed so far. Due to these limitations, it is also not possible to establish beyond doubt any underreporting suspected here. For this, a reclassification of all PTs would have to take place and, in addition, a more detailed analysis of the differences than is possible within the scope of this work.

The results show that there are some interesting differences can be seen. These differences seem to be partly very clear, but due to the various restrictions in the chapters, it is not possible to make generally valid statements.

6. Conclusion

After this short summary of the results and problems, a short outlook is given here. Although there are already suggestions on how AEs should be presented in publications, there are no fixed guidelines yet. Therefore, it would be desirable to have generally applicable criteria that must be taken into account in publications. This would also lead to a better comparison of publications with each other and important information on occurring side effects could already be obtained from them. Since this is not yet the case, the AE criteria are sometimes only barely or not at all met in publications, as can be seen with the papers “Lobar or Sublobar Resection for Peripheral Stage 1A Non-Small-Cell Lung Cancer”[21] fulfilling no criterion and the paper “Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer”[17] fulfilling only two criteria. One reason for this is that benefits have a greater positive influence on the sale of a drug. To ensure this, a checklist could be drafted, similar to the CONSORT group statement, which, however, only takes into account the presentation of AEs in publications. Furthermore, criteria should be defined that must be fulfilled for the paper to be published. Although the CONSORT criteria and extensions of them already exist, they are not sufficient in that they are only taken into account for the publication. Since many decisions are already made during the preparation of the study that have a major impact on the publication, these should also be taken into account there. Therefore, it would be desirable to create combined guidelines from ICH guidelines and CONSORT statement, which cover all phases of a study including publication. However, it would be beyond the scope of this paper to describe what this could look like.

Although there are already recommendations for the presentation of AEs in publications, as can be seen by the CONSORT statement and its extensions, there is still some potential for improvement, as shown in the thesis. The goal should therefore be to continue to strive for improvements in this area as well, if only by taking the points mentioned in this paper into account in publications and including them in their preparation.

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I hereby declare that I have written this Bachelor's thesis independently without the help of third parties and without using any sources or aids other than those indicated. All passages taken verbatim or in spirit from the sources used are marked as such individually.

This thesis has not yet been submitted to any other examination authority and has not been published.

I am aware that a false declaration will have legal consequences.

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