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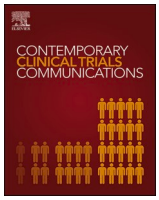

Estimands in CNS trials – A review of strategies for addressing intercurrent events

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ABSTRACT

Background: The estimands framework represents a significant innovation for the design, conduct, analysis, and interpretation of clinical trials. An aim of the framework is to increase precision and transparency on the handling of intercurrent events (IEs), defined as events occurring after treatment initiation and affecting the endpoint. While the experience in constructing and reporting estimands in the published literature is limited, developers performing confirmatory studies are already making use of the new paradigm, allowing to survey the strategies proposed by applicants and endorsed by regulators.
Methods: To identify strategies for handling IEs in confirmatory central nervous system (CNS) trials, we searched scientific advice letters issued by the European Medicines Agency (EMA) between 2017 and 2022. We developed a categorisation of the IEs and classified, according to the strategies defined in the framework, the strategies proposed by the Applicants and recommended by the agency. Strategies proposed and recommended were summarised by category of IEs, and the rationale for the choices was analysed qualitatively.
Results: In total, 170 IEs were identified in 52 confirmatory trials. A clear preference for the treatment policy strategy for treatment discontinuation and for the hypothetical strategy for pandemic-related disruptions was identified. For other categories of IEs, there are more mixed patterns.
Discussion: This study highlights the multidimensional nature of choosing a strategy for an IE. For different occurring IEs in confirmatory CNS trials different strategies are of regulatory interest, depending on the trial objective, underlying disease properties, rarity of disease, as well as frequency and timing of IEs and their relatedness to the disease.

1. Introduction

The introduction of the estimands framework [1] has represented a significant innovation for the design, conduct, analysis, and reporting of clinical trials, with the potential to increase the clarity on the trial objective and of what the effect estimated by the trial targets [2,3].

The estimand is defined by its attributes (treatments, population, endpoint, IEs, and population-level summary), which incorporate a principled and transparent approach to handle intercurrent events (IEs), defined as events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Participants in clinical trials might, for example, discontinue the treatment they are assigned to, or start another (non-) pharmacological intervention. The strategies described in the addendum to deal with the IEs are.

- Treatment policy, considering that all observations are directly relevant to inform the treatment effect irrespective of the IE,
- Hypothetical, where the interest lies in the treatment effect in a hypothetical scenario in which the event would not occur,
- Composite, when the IE represented a (usually negative) outcome in itself (often implemented by integrating the event in a composite definition of the endpoint),
- Principal stratum, defining the population of interest as the one in which the event would or would not occur under a certain treatment assignment or regardless of the treatment assignment,
- While on treatment, restricting the observation time of interest to before the occurrence of the IE.

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Abbreviations

AD –	Alzheimer's disease
ALS –	Amyotrophic lateral sclerosis
CNS –	Central nervous system
DMD –	Duchenne muscular dystrophy
EMA –	European Medicines Agency
IE –	Intercurrent event
ICH –	International Council for Harmonization
MDD –	Major depressive disorder
MS –	Multiple sclerosis
PD –	Parkinson's disease
SA –	Scientific advice
SAWP –	Scientific advice working party
SMA –	Spinal muscular atrophy

The IEs and their strategies are to be included in the formulation of a clinical question of interest. For example, one might be interested in the effect of a disease-modifying treatment for Alzheimer's disease regardless of its discontinuation (treatment policy) but in the hypothetical scenario of no use of symptomatic medications (hypothetical). The clinical question of interest is then translated into an estimand, where the attributes are clearly spelled out. As a subsequent step, statistical estimators are then selected in line with the strategies chosen.

For specific CNS disorders, some publications on the thinking process for defining an estimand [4], or on the methods of estimation aligned to certain strategies [5,6] exist, and some regulatory guidance that includes strategies to account for intercurrent events has been given [7,8]. However, the experience in constructing and reporting estimands is in general limited [9].

In this review, we aim to summarise which strategies developers proposed and which strategies EMA endorsed – in the context of requests for scientific advice - for commonly occurring IEs in CNS trials, and to highlight some of the elements that influenced the choices made.

2. Methods

For extracting information about IEs and strategies for handling these proposed by developers and recommended by EMA in the context of scientific advice, we searched in the scientific advice letters' database of the EMA for letters issued - after the publication of the Addendum in October 2017 - between 1 January 2018 and 31 December 2022. We used keywords related to estimands and IEs (see supplementary material) and names of commonly studied CNS diseases, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD), epilepsy, major depressive disorder (MDD), multiple sclerosis (MS), Parkinson's disease (PD), schizophrenia, and spinal muscular atrophy (SMA). The resulting letters were screened for eligibility according to the following criteria: (i) concerning confirmatory efficacy studies in CNS diseases and (ii) including reference (at least in the response) to IEs and their handling. Background information submitted (including protocol synopses and full protocols) were used when needed to extract information. For each confirmatory trial, we first extracted as unstructured text all the parts of the questions and answers relating to the estimands. The categorisation of IEs was initially done as open coding – staying as close as possible to the wording found in the letters. Subsequently, these initial codes were reviewed, also in light of the wordings used in publications and guidance documents, and a focus coding was adopted, resulting in the following categories.

- treatment discontinuation,
- changes or initiation of additional/concomitant therapies,
- use of alternative therapies that cannot be co-administered,
- death,
- dose interruption,
- pandemic-related disruptions,
- other IEs.

The categorisation of the strategies, on the other hand, was according to the strategies defined in the Addendum. All the categorisations were primarily done by LM and subsequently reviewed by LG. Disagreements or complex cases were further discussed and agreed by LM, LG, and FL. Furthermore, where provided, the justifications for the choice of strategy were recorded.

For each of the IE categories, the number of times each of the strategies was proposed by the developers and suggested by EMA was calculated. Results were visualised as alluvial plots, where each lane visualises the trajectory for an IE in a trial, from the proposal of the developer to the advice of EMA. IEs for which the developers had not clearly stated a strategy were still included if EMA suggested one. In this case, the strategy proposed is reported as N/A. The plots were generated using R version 4.2.2, with the packages ggalluvial [10,11], ggplot2 [12], and scales [13].

3. Results

3.1. Identified IEs in confirmatory CNS trials

Systematic searching in EMA's scientific advice database for strategies to address IEs in CNS trials identified 80 scientific advice letters describing 82 confirmatory trials (Fig. 1A). In 30 cases identified by the search, no IEs were described in the study protocol but the use of the estimands framework was recommended by EMA, which led to the identification of these letters by the targeted search. The vast majority of the remaining 52 trials were superiority trials (n = 50), with one equivalence and one non-inferiority trial. In these study protocols, 190 IEs were identified in total, however in 20 cases no strategy could be identified in the responses provided by EMA, generally due to lack of sufficient background information provided by the developers. Ultimately, 170 IEs for which at least an EMA recommendation on the strategy could be extracted were grouped in the seven above-mentioned categories and included in the descriptive analyses (Fig. 1B). Some trials have described more than one IE belonging to the same category of IEs (for example, treatment discontinuation due to different reasons handled differently), resulting in the analysed number of IEs showed in Fig. 1B. The IE considered most often was treatment discontinuation (discussed at least once in 47 out of 52 trials), followed by additional treatment (in 28 out of 52 trials), alternative treatment (in 15 out of 52 trials), death (in 14 out of 52 trials), dose interruption (in 10 out of 52 trials), pandemic-related IEs (in 5 out of 52 trials), and other IEs e.g. relapse, seizure, protocol deviation, and occurrence of adverse events (in 5 out of 52 trials).

3.2. Strategies addressing treatment discontinuation

A total of 47 trials included 68 IEs classified into the 'treatment discontinuation' category. Contrary to the proposed strategies of the developers, in most cases EMA recommended to handle treatment discontinuation with a treatment policy strategy (Fig. 2). However, in few cases other strategies have been agreed to, namely the hypothetical, composite, while on treatment, or principal stratum strategy. The composite strategy was used in a non-inferiority trial for handling treatment discontinuation due to lack of efficacy, adverse events, and other reasons as co-primary estimand together with the treatment policy strategy. The while on treatment strategy has been accepted for investigating the symptomatic character of a treatment but with the advice to additionally investigate the effect defined with the treatment policy strategy for treatment discontinuation. The principal stratum strategy was only accepted in a single case of an equivalence study.

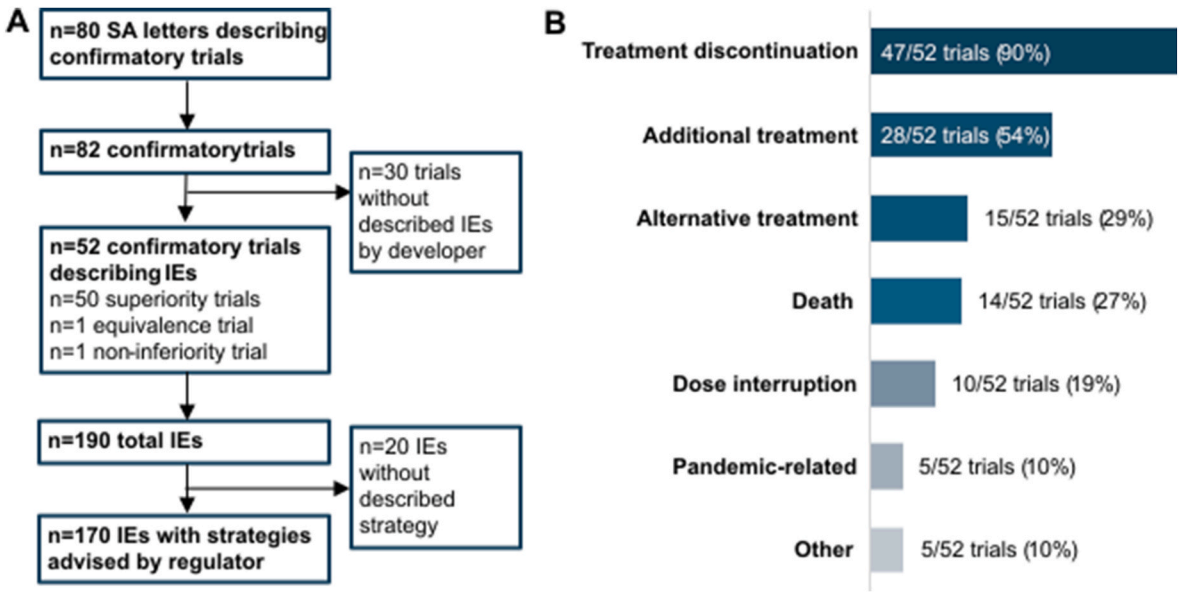

Fig. 1. Identified intercurrent events in confirmatory CNS trials. A: *The flow chart shows the number of identified scientific advice (SA) letters with* a priori *position on strategies to handle intercurrent events (IE) in confirmatory CNS trials. Note that one letter may relate to more than one trial and that on each one trial advice might be sought on the handling on more than one IE. 170 IEs were sorted into the categories treatment discontinuation (n = 68), additional therapy (n = 40), alternative therapy (n = 18), death (n = 16), dose interruption (n = 11), pandemic-related (n = 10) and other IEs (n = 7).* ***B:*** *Chart illustrates the categories with corresponding numbers of identified confirmatory CNS trials describing IEs. Note that some trials have described different IEs that belong to the same category.*

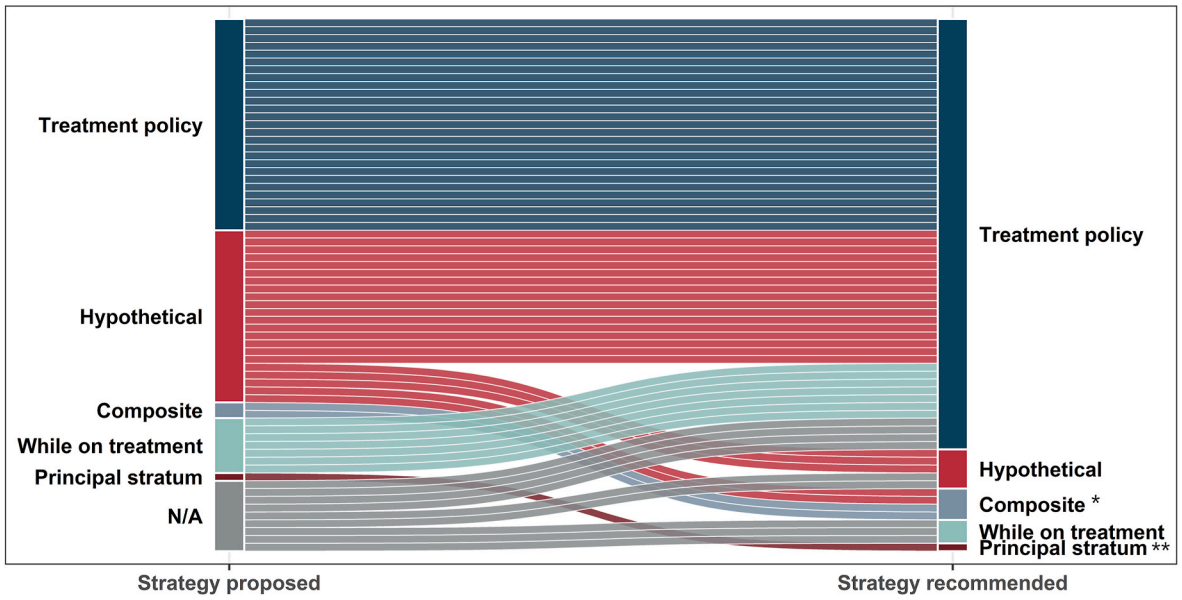

Fig. 2. Strategies to handle treatment discontinuation. Each lane of the alluvial plot visualises the trajectory of the strategy for handling treatment discontinuation in a trial, from the proposal of the developer to the advice of EMA. Note that in some studies no strategy for handling IEs was declared (labelled "N/A), but a recommendation was made in the scientific advice letter. *In the non-inferiority trial the composite strategy was recommended as co-primary approach together with treatment policy. **In the equivalence trial, principal stratum was endorsed.

3.3. Strategies addressing additional therapy

40 IEs relating to 'additional therapy' were described in 28 trials. For changes in concomitant therapy (e.g., symptomatic or non-pharmacological therapy), a treatment policy strategy was primarily recommended by regulators with few exceptions (Fig. 3). In superiority trials for Alzheimer's Disease (AD) at different stages, the hypothetical strategy was agreed for targeting an effect in absence of symptomatic treatments.

3.4. Strategies addressing alternative therapy

In total, 15 trials described 18 IEs categorised in relation to alternative, non-concomitant therapy. In general, no strategy is clearly preferred to be used in estimating the treatment effect if changes in alternative therapy are occurring (Fig. 4). Interestingly, studies of psychiatric disorders (major depressive disorder, schizophrenia, or obsessive-compulsive disorder) a hypothetical strategy was considered as more regulatory relevant.

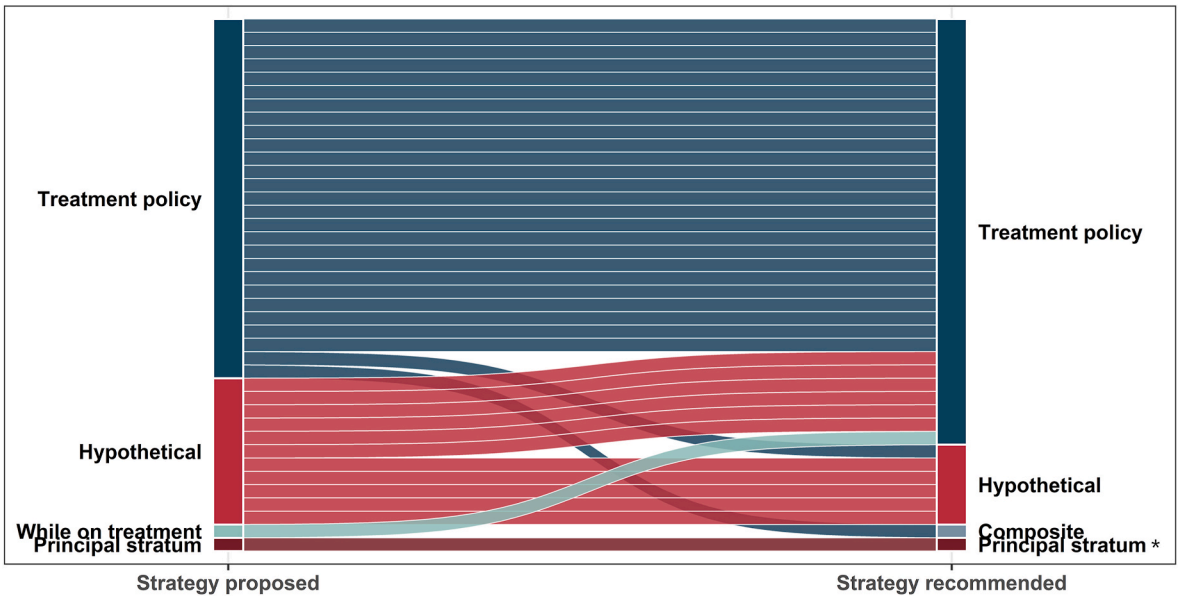

Fig. 3. Strategies to handle additional therapy. Each lane of the alluvial plot visualises the trajectory of the strategy for handling the use of additional therapy in a trial, from the proposal of the developer to the advice of EMA. *In the equivalence trial, the principal stratum strategy was endorsed.

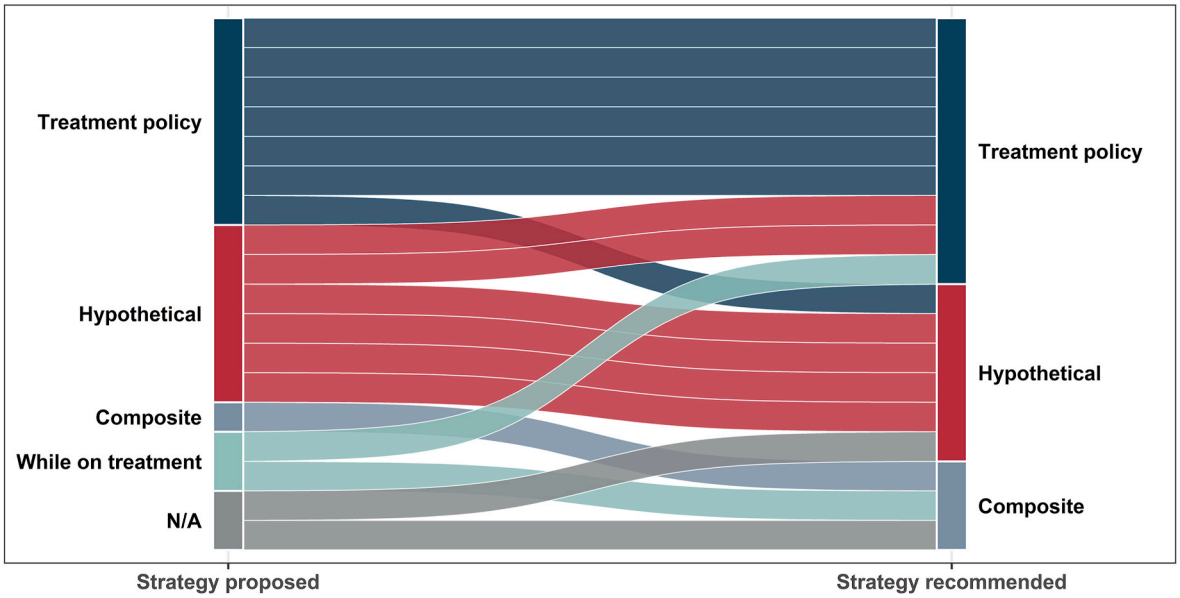

Fig. 4. Strategies to handle alternative therapy. Each lane of the alluvial plot visualises the trajectory of the strategy for handling the use of alternative therapy in a trial, from the proposal of the developer to the advice of EMA. Note that in some studies no strategy for handling intercurrent events was declared (labelled "N/A), but a recommendation was made in the scientific advice letter.

3.5. Strategies addressing death

The IE of death was described 16 times in 14 trials. Different strategies were endorsed for the event of death depending on the study setting (Fig. 5). Generally, if death was related to the underlying disease as in neurodegenerative disorders, the composite strategy was the preferred choice of regulators. Both the while on treatment and hypothetical strategy were only agreed to in rare diseases, or if death was clearly unrelated to disease.

3.6. Strategies addressing 'pandemic-related IEs'

As in the recent years especially the COVID-19 pandemic has affected clinical trials significantly, pandemic-related disruptions were considered an IE when describing estimands in clinical trial protocols and advice requests. A total of 5 trials included 10 times pandemic-related IEs. In most of the cases, the hypothetical strategy was suggested as regulatory relevant strategy for estimating the treatment effect in CNS trials (Fig. 6). For one study, the impact of the pandemic on missing doses was split in two different IEs depending on the quantity of doses missed, and a treatment policy strategy was endorsed for the IE referring to lower number of doses missed.

3.7. Strategies addressing dose interruptions

IEs categorised into 'dose interruptions' (n = 11) were described in 10 studies. In all superiority trials, dose interruption was recommended to be handled with an estimand addressing the treatment policy strategy

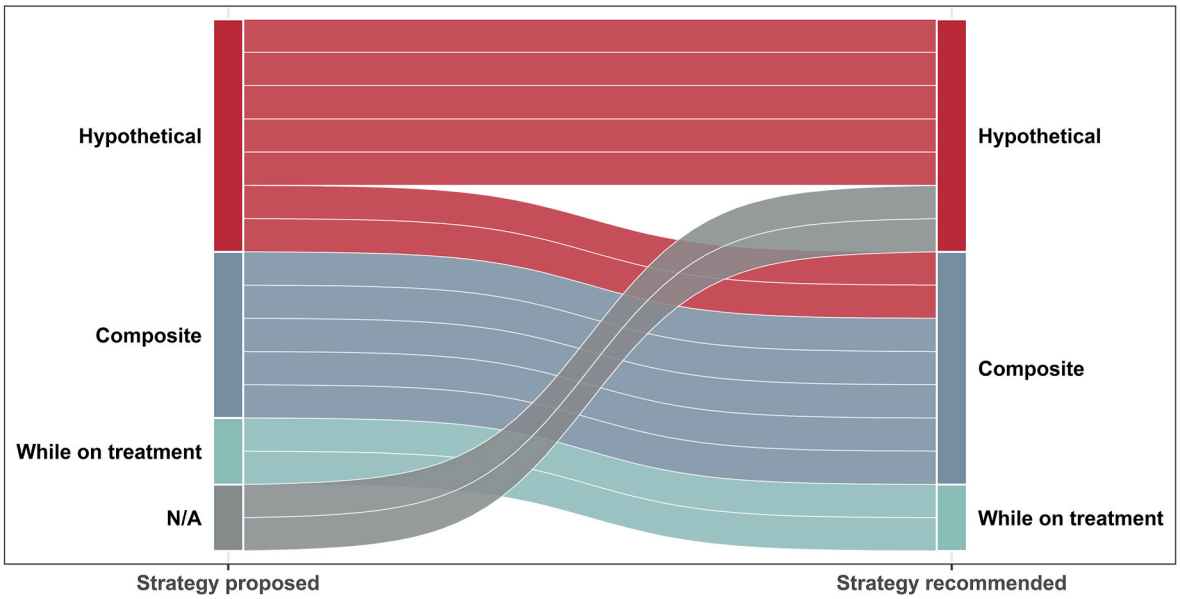

Fig. 5. Strategies to handle death. Each lane of the alluvial plot visualises the trajectory of the strategy for handling death in a trial, from the proposal of the developer to the advice of EMA. Note that in some studies no strategy for handling intercurrent events was declared (labelled "N/A), but a recommendation was made in the scientific advice letter.

Fig. 6. Strategies to handle pandemic-related IEs. Each lane of the alluvial plot visualises the trajectory of the strategy for handling pandemic-related IEs in a trial, from the proposal of the developer to the advice of EMA. Note that for this IE data is only available from 2020.

(Suppl. Fig. 1). In contrast, the composite strategy was endorsed in a non-inferiority study but with the recommendation to define a co-primary estimand using the treatment policy strategy.

4. Discussion

This study revealed that for the most common IEs in confirmatory CNS trials different strategies may be of regulatory interest. The choice among these strategies depends on trial objective, underlying disease properties, therapeutic context, as well as frequency and timing of IEs and their relatedness to the disease or treatment.

The lack of a clear one-to-one correspondence between categories of IEs and strategies – both in the proposals from the developers and the recommended strategies from regulators – highlights the multidimensional nature of choosing an estimand. Firstly, the disease context plays a role. An example is the use of additional medications, which is often seen as part of a treatment strategy of which the investigational medicine is part, and as such is handled through a treatment policy strategy. However – and in line with a possibility outlined in the Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease [7] – in specific cases in neurodegenerative disorders a hypothetical approach has been accepted for the initiation of symptomatic medications (which can be used in addition to the investigational ones) when disease-modifying treatments were being investigated. Affirmed by our findings, for the event of alternative therapy the hypothetical strategy might be also of regulatory relevance in the context of psychiatric disorders. This might reflect a clinical context where the investigational agent is one of several clinically available

options, and the comparison of interest for approval is with a regimen not including the other agents. This is echoed in the recent Guideline on clinical investigation of medicinal products in the treatment of depression [8]. Secondly – and as far as it can be concluded given the low numbers of non-superiority trials in our analysis – it appears that the study objective – superiority, non-inferiority or equivalence – may affect the applied strategy to define the treatment effect, as also mentioned in the Addendum [1]. For instance, the treatment policy strategy for handling treatment discontinuation is of high regulatory interest in a superiority trial, whereas in an equivalence study inclusion of data after discontinuation could – depending on the specific data-generating mechanism – make the treatment effect of the study drug appear more similar to the effect of the comparator. In non-inferiority and equivalence trials, co-primary estimands were used in the few cases included in our analysis, which might reflect the former common practice of analysing both the intention-to-treat and the per-protocol datasets. Given the limited sample size in this category of studies, further investigations across therapeutic areas seem appropriate.

In general, we do not have a high number of cases where a principal stratum strategy was endorsed. This might be for different reasons. Firstly, we have limited our research to strategy for the primary estimands. While the principal stratum strategy can have important roles in drug development, increasing our understanding of the treatment effect, it will typically not be of primary interest [14], as the primary benefit/risk evaluation is generally on all patients to whom the medicine would be prescribed. Secondly, as also acknowledged in the Addendum [1], estimating an effect in a principal stratum requires strong, untestable assumptions. While there are specific situations where plausible sets of assumptions justify simple estimators [15,16], this is often not the case.

Furthermore, the question of whether the IE was associated with the disease or the treatment was also a factor considered in deciding on the strategy. It was often the case that the advice letter recommended robust ascertainment of the reason leading to the IE, including with supplementary analyses, especially when the reason for the occurrence of the IE influenced the choice of strategy. For the intercurrent event 'death', the hypothetical or a while on treatment strategy were accepted in some of the cases where a strong belief of unrelatedness to treatment and disease course was held.

In accordance with guidance issued by EMA [17], pandemic-related disruptions to trial conduct (leading, for example, to missed visits and/or dose interruptions) were often discussed as IEs in the estimands framework. Here, we observed a tendency to endorse the hypothetical approach to reflect the treatment effect in a world without the acute effects of the early waves of the COVID-19 pandemic. This endorsement was often accompanied by the recommendation that the IEs had to be truly and solely attributable to the pandemic (and not, for example, to the health state of the participants).

The finding that in 30 of the 82 letters identified the Estimand framework was not used by the developer but recommended by EMA is to be interpreted with caution. It is often the case that advice is sought at early stages of planning a trial, and it is possible that some of the developers were already planning to specify an estimand. On the other hand, this high proportion might point to the difficulties that some developers have been encountering at this early stage of implementing the framework. Pointing in the same direction, we have found that often the estimand is not well reported in protocols and in scientific advice requests, but often mixed with the description of the estimator, and especially with the handling of missing data. Furthermore, study protocols do often not include a detailed justification for the choice of strategies, nor they address the expected frequency, timing, and distribution of IEs, which might also inform the appropriateness of methods for estimating a treatment effect. It is also noteworthy that in some study protocols the term sensitivity analysis was incorrectly used to refer to either supplementary analysis or different/secondary estimands. As per the Addendum [1], sensitivity analysis is aligned to the same target of estimation and helps to examine the robustness of the estimate in the presence of deviations from different assumptions used in the statistical model for the main estimator. In contrast, secondary estimands and supplementary analyses can further characterise a treatment effect, by aiming other targets of estimation. To a certain extent, it is possible that also the rate of disagreement between developers and EMA might be a sign of the early stages of implementation of the framework.

Regulators, in this context, could enhance their support to developers in the implementation of the estimands framework. This includes publishing – as done in the Alzheimer's Disease guideline [7] and in the draft Guideline on depression [8] – reflections on disease-specific implementation of the framework in their development guidelines. Additionally, use of templates that guides a transparent reporting of estimands for protocols and other documents might be helpfully supported (in this direction, the ongoing work on the ICH M11 clinical study protocol and technical specifications is of note).

A few study limitations are inherent to our methodology and to our use of the EMA's scientific advice database as source of data. Firstly, only scientific advice letters were included in which the developer or regulator described terms of IEs or estimand strategies. Given the search strategy adopted – we cannot quantify the number of cases where neither the developer nor the scientific advice mentioned estimands and IEs. In addition, this may lead to a miss-representation of certain types of IEs and estimand strategies found in the present study, and over-represent cases were the definition of the estimand was complex enough to deserve being raised as a topic for Scientific Advice. In particular, the use of the composite strategy may be underestimated if applicants' IE have been addressed with a composite strategy and directly included in the endpoint without explicitly discussing it as an IE. Lastly, the rather broad categorisation of IEs might also represent a conceptual limitation.

In conclusion, our review outlined the strategies accepted by regulators for IEs in CNS trials, and indicated various ways in which the application of the estimands framework can be further improved. On the one side, there is a need for improvements to the study protocol in terms of a clearer definition of IEs and estimands, with a clear distinction between the discussion on the estimand and the discussion on the estimator, including methods for handling of missing data. On the other side, detailed guidance on the implementation of the estimand framework in specific diseases seem to be necessary. Developers are therefore highly encouraged to seek for an early dialogue with regulators using the Scientific Advice platform, to clarify the estimand that is relevant for regulatory decision-making in their specific setting. Taken together, this will help to provide more clarity on the estimated treatment effect to conduct higher quality studies that will improve the evidence on which medicines are evalauted.

Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Contributions

LM, FL and LG contributed to the conception, design and drafting of the manuscript. LM performed data acquisition and compilation. BD contributed to the interpretation of the findings and the drafting of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101266.

References

[1] ICH, Addendum on Estimands and Sensitivity analysis in clinical trials, 31/03/2023]; Available from: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf, 2017.
[2] B.C. Kahan, et al., Eliminating ambiguous treatment effects using estimands, Am. J. Epidemiol. (2023) kwad036.
[3] M. Jin, G. Liu, Estimand framework: delineating what to be estimated with clinical questions of interest in clinical trials, Contemp. Clin. Trials 96 (2020) 106093.
[4] E. Polverejan, et al., Defining clinical trial estimands: a practical guide for study teams with examples based on a psychiatric disorder, Therapeutic Innovation & Regulatory Science (2023) 1–29.
[5] A. Noci, et al., A comparison of estimand and estimation strategies for clinical trials in early Parkinson's disease, Stat. Biopharm. Res. 15 (3) (2023) 491–501.
[6] E. Polverejan, V. Dragalin, Aligning treatment policy estimands and estimators—a simulation study in Alzheimer's disease, Stat. Biopharm. Res. 12 (2) (2020) 142–154.
[7] EMA, Guideline on the Clinical Investigation of Medicines for the Treatment of Alzheimer's Disease - Revision 2, 2018 [cited 2023 22/05/2023]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicines-treatment-alzheimers-disease-revision-2_en.pdf.
[8] EMA, Draft Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression, 2023 [cited 2023 23/10/2023]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-investigation-medicinal-products-treatment-depression-revision-3_en.pdf.
[9] B.C. Kahan, et al., Estimands in published protocols of randomised trials: urgent improvement needed, Trials 22 (2021) 1–10.
[10] J.C. Brunson and Q.D. Read, Ggalluvial: Alluvial Plots in 'ggplot2, 2023. R package version 0.12.4.
[11] J.C. Brunson, Ggalluvial: layered grammar for alluvial plots, J. Open Source Softw. 5 (49) (2020) 2017.
[12] V. Gómez-Rubio, ggplot2-elegant graphics for data analysis, J. Stat. Software 77 (2017) 1–3.
[13] H.S.D. Wickham, Scales: Scale Functions for Visualization, 2022.
[14] B. Bornkamp, et al., Principal stratum strategy: potential role in drug development, Pharmaceut. Stat. 20 (4) (2021) 737–751.
[15] B.C. Kahan, et al., Using modified intention-to-treat as a principal stratum estimator for failure to initiate treatment, Clin. Trials 20 (3) (2023) 269–275.
[16] Y. Lou, M.P. Jones, W. Sun, Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data, J. Biopharm. Stat. 29 (1) (2019) 151–173.
[17] EMA, Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials [cited 2023 22/05/2023]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf, 2020.