

How limited are Limitations?

Traversing across biomedical publications

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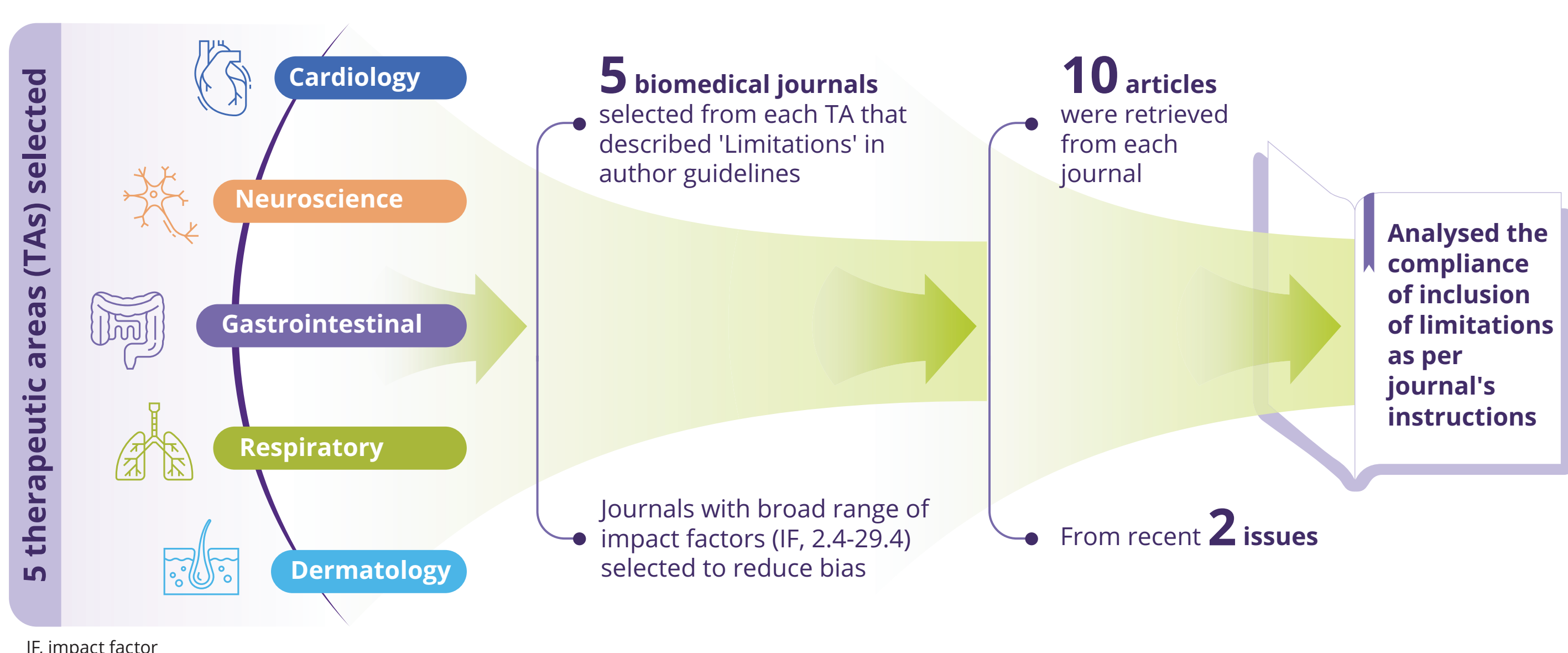
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BACKGROUND

- Inclusion of relevant study limitations plays a pivotal role in providing a meaningful context for the interpretation or generalisability of research outcomes and conclusions.¹
- The International Committee of Medical Journal Editors (ICMJE),² journal guidelines, and other publication guidelines^{3,4} recommend the inclusion of study limitations in biomedical publications to ensure an unbiased and transparent perspective of the research findings. However, study limitations are often inadequately reported in research articles, causing an important deficit of context for the scientific literature.^{5,6}
- This analysis aimed at identifying the extent and categories of limitations captured in published articles from randomised controlled trials (RCTs), patient database/registries, and observational trials (OBTs).

METHODS

Figure 1: Study design

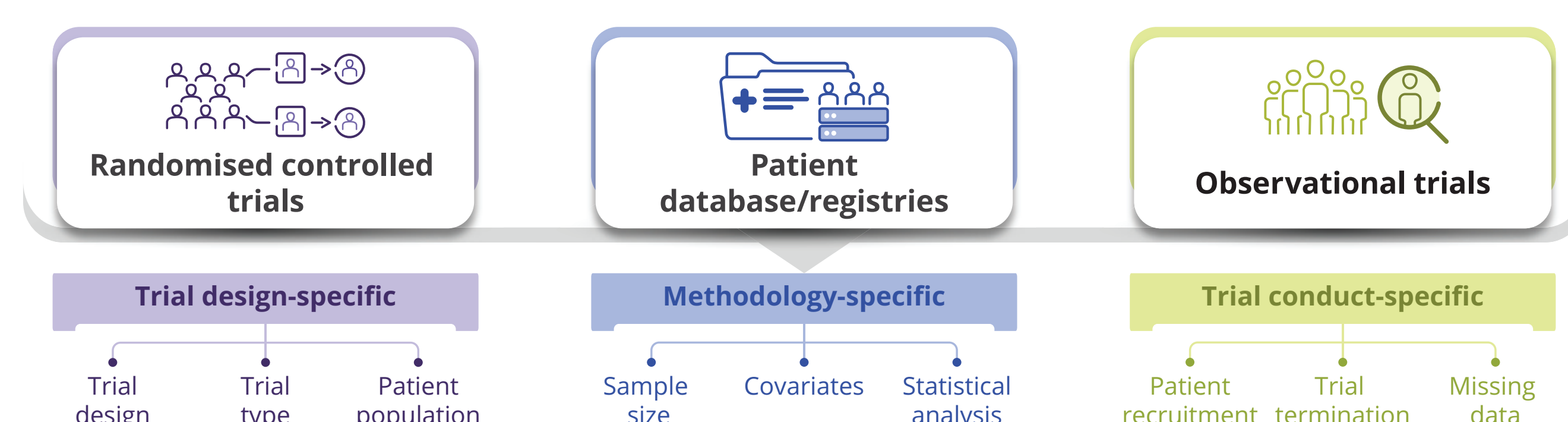


CONCLUSIONS

- Our findings demonstrate that 77% of the published articles showed transparency in reporting limitations.
- All categories of limitations were better represented in RCTs and OBTs than in database/registry trials.
- Further investigations into limitation types involving more articles, and different trial designs are warranted for identifying gaps, enhancing reproducibility and generalisability of findings, and improving reporting standards of biomedical publications across study types.

- Total 15 articles each of RCTs, patient database/registries, and OBTs were further assessed to identify the categories of limitations (Figure 2).

Figure 2: Specific limitations evaluated for randomised control trials, database/registries, and observational trials



- The placement of limitations at specific locations in the articles, as per journal instructions, was analysed.
- Statistical data were reported as percentage values, and all the analyses were carried out by therapeutic area (TA) and study type.

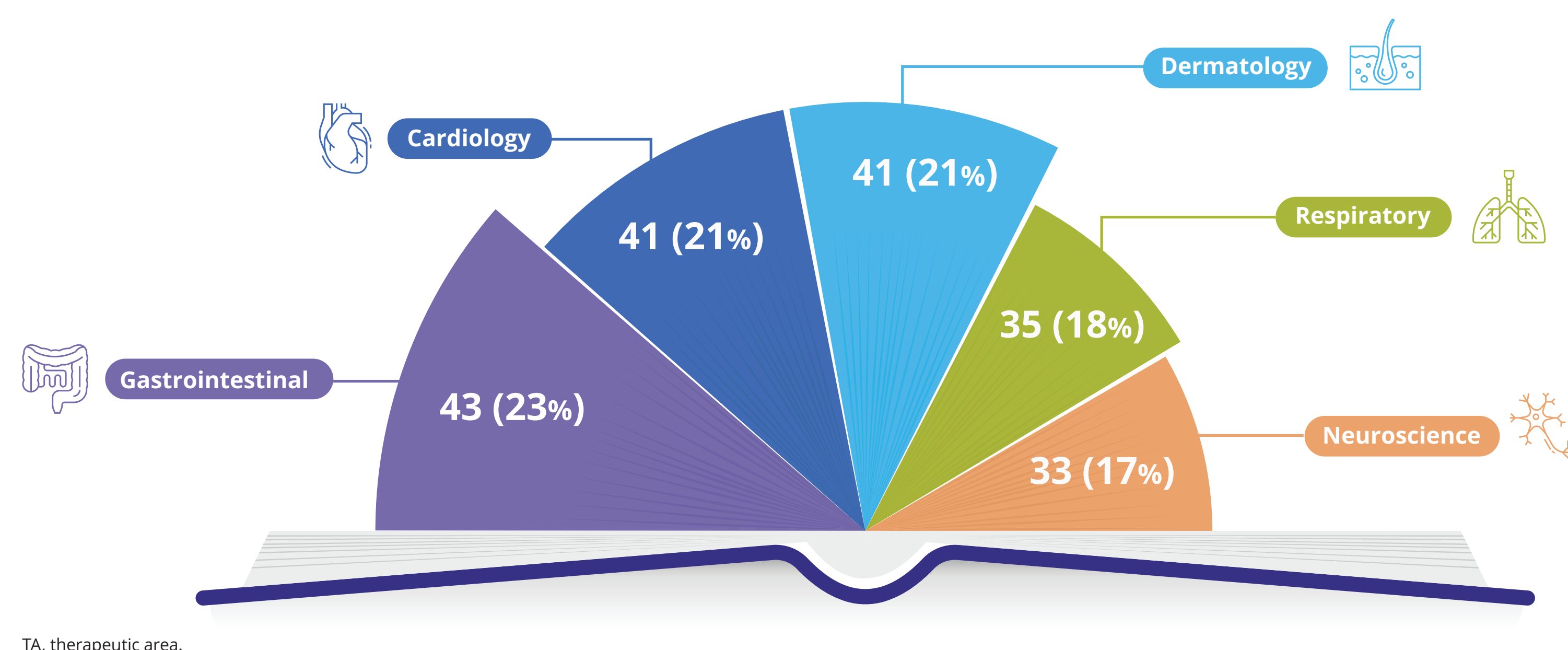
RESULTS

- Out of the total 250 published articles screened (50 per TA), 193/250 (77%) articles showed compliance for inclusion of study limitations as per journals' instructions.

Analysis by therapeutic area

- Among all TAs, most (43/193; 23%) articles from gastrointestinal had included limitations, whereas neuroscience had the least number of articles (33/193; 17%) featuring limitations (Figure 3).
- In cardiology, gastrointestinal, and neurosciences, 1 journal each contained all (10/10; 100%) articles with study limitations.

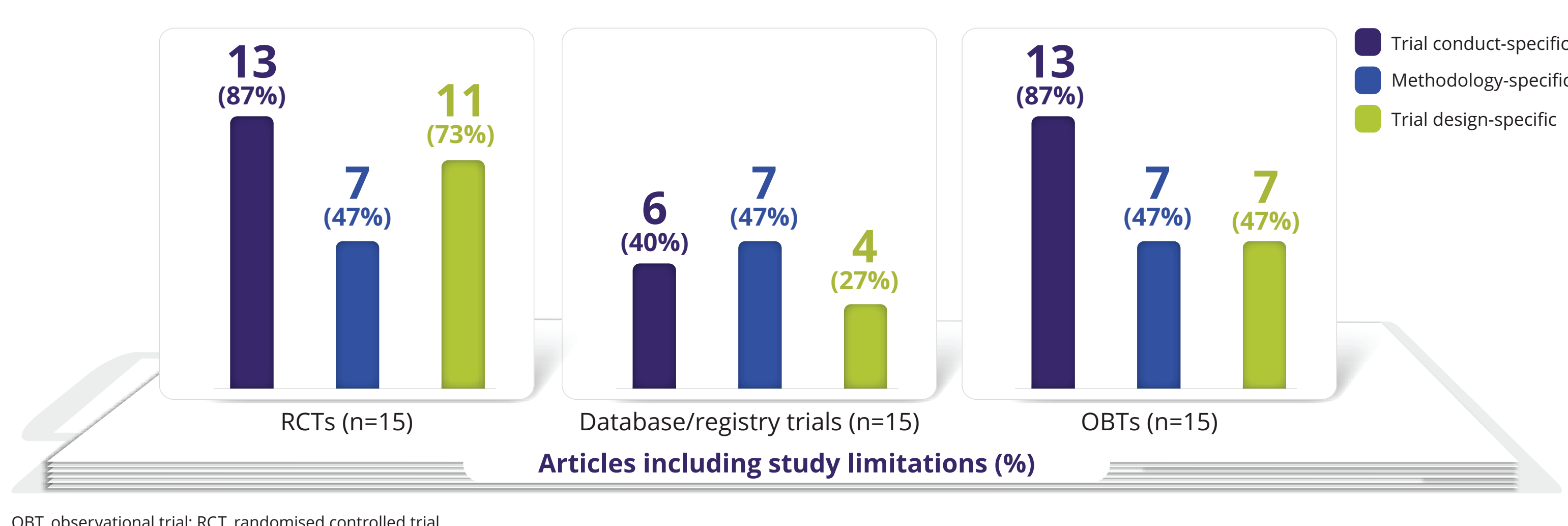
Figure 3: Inclusion of limitations in articles per TA (n=50 per TA, N=250)



Categorisation of limitations by study type

- Further analysis of 45 articles (15 each) for RCTs, database/registry trials, and OBTs showed that methodology-specific limitations were reported in similar proportions (47%) among the trials, while trial design-specific (27%) and trial conduct-specific limitations (40%) were reported in less proportion in database/registry trials (Figure 4).

Figure 4: Inclusion of study limitations by article type (N=250)



- Certain limitations were similar across the types of trials (Table 1).

Table 1: Summary of limitations included in the trials (n=45)

	Trial design-specific	Methodology-specific	Trial conduct-specific
RCTs	- Not a prospectively planned analysis - Open-label study design, patients not blinded Single center - Non-prespecified post hoc analysis - Absence of a placebo-controlled trial	- Variables not measured Not adequately powered for race-based stratified analyses - Limited racial diversity - Inherent imprecision Degree of bias	- Adjudication bias - Standard procedures not followed Missing data - Crossovers Non-generalisability of results - Inability to determine parameters
Database/registry trials	- Data from national database; findings can't be generalised - Large cohort study, can't obtain detailed individual patients data - Retrospective analysis without preestablished follow-up assessment and management Unicentric nature	- Included restricted population - Standard process not followed - Ethnic variation - Confounding factors - Retrospective analysis without preestablished follow-up assessment and management Small sample size - Missing variables Risk of selection bias - Bias in statistical analysis	Non-generalisability of results - Heterogenous results - Potential misclassification bias - Disease ascertainment based on ICD9/10 codes - Inadequate patient management
OBTs	- Predefined analysis based on previously published data - Interim analysis - Observational study or retrospective analysis; some data missing Single center - Uncontrolled design	Small sample size - Unable to determine cause and effect Analysis not powered to detect differences Reduced statistical power Selection bias - Limited number of covariates	- Hypothesis-generating data Non-generalisability of results - Misclassification bias Missing data - Standard conditions not used - No formal follow-up appointment

Similar limitations across studies are presented in bold
ICD, International Classification of Diseases; OBT, observational trial; RCT, randomised controlled trial.

Placement of limitation section basis journal-specific guidelines

- Most of the articles showed compliance in adding the limitation section at the suggested location per journal instructions (Table 2).

Table 2: Placement of limitations in the articles in compliance with journal instructions (N=250)

Placement of limitations	n (%)
In a box in the manuscript	10/10 (100%)
Separate section between discussion and conclusion	32/40 (80%)
In the abstract	8/10 (80%)
As a separate paragraph	124/180 (69%)
As a subheading in the discussion section	3/10 (30%)

Categorisation of limitations by impact factor

- No considerable difference was noted in reporting limitations when the articles were stratified basis high impact factor (≥ 6 ; 72/90 [80%]) or low impact factor (< 6 ; 121/160 [76%]) journals.

Limitations

- In this study, only 45 articles were analysed for the trial design-specific, methodology-specific and trial conduct-specific limitations.

Disclosures

All authors are employees of SIRO Clinpharm Pvt. Ltd.

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