

BACKGROUND

- ClinicalTrials.gov (CT) is a web-based resource that provides patients, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. [1]
- Provided free of charge downloadable snapshots of CT database contains the full information available on the CT website.
- However, due to the relational structure opens up a great potential for exploration of the whole database content beyond the limitations imposed by the CT's web-based search interface.
- Rapidly evolving area of gene therapies provides opportunity to treat medical conditions, for which the available interventions are ineffective, or no intervention exist. CT database mining was used as a method to follow the progress status of advanced gene therapies.

OBJECTIVE

The aim of this analysis was to characterise design and status of advanced gene therapies (GTs) clinical trials.

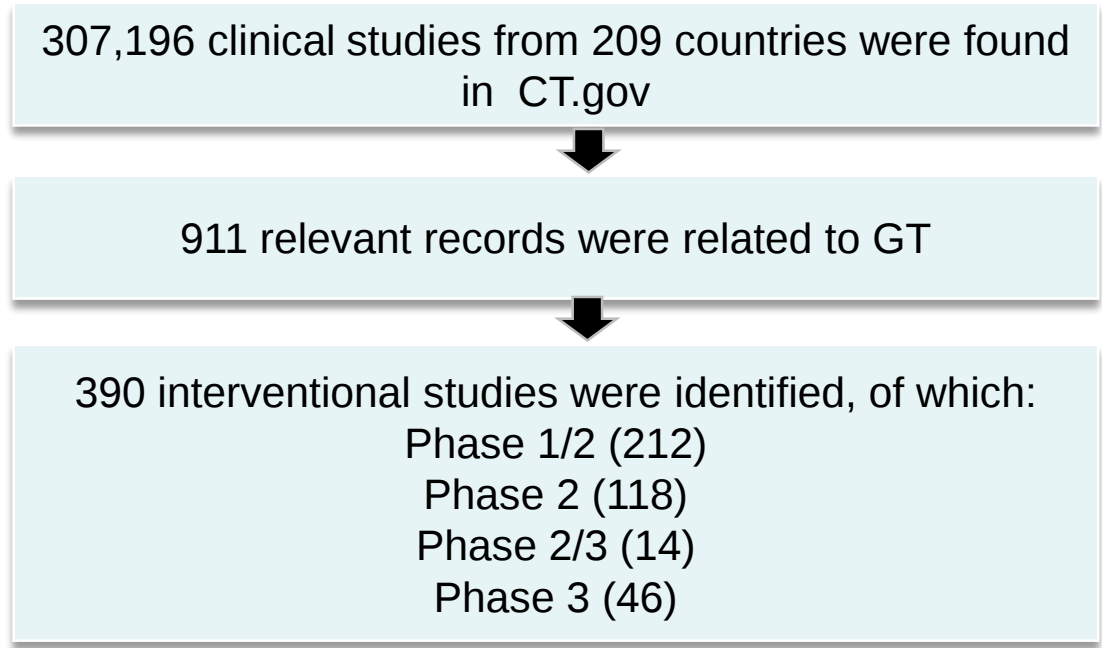
METHODS

- CT database snapshot (as at June 1, 2019) was downloaded through the link provided on the Clinical Trials Transformation Initiative webpage. [2]
- Uncompressed 44 flat pipe-delimited files (total size >5.7GB) were used to populate relational database, comprising information about 307,196 clinical studies from 209 countries.
- The largest file was related to reported events (>1.5GB) and the outcome measurements (~1.2GB).
- Relevant records were retrieved if they contained at least one of the following phrases: “gene therapy”, “gene transfer” or “AAV” (adeno-associated vectors) located in tables containing information about: trial keywords, title, summary, study description, interventions, study design, outcomes and participant flow.
- Record-specific data related to title, study description, study design, presumed and actual timeframes, eligibility criteria, enrolment, health condition, interventions, outcomes and results were automatically transferred to excel spreadsheet for further analysis.
- The database mining was performed using Creativ-Ceutical in-house search engine written in R language. [3]
- A descriptive analysis was conducted to summarise the distribution of advanced gene therapy studies in terms of methodological design, study phase, designations and clinical relevance of the primary outcomes, as assessed by the analyst (WY).

RESULTS

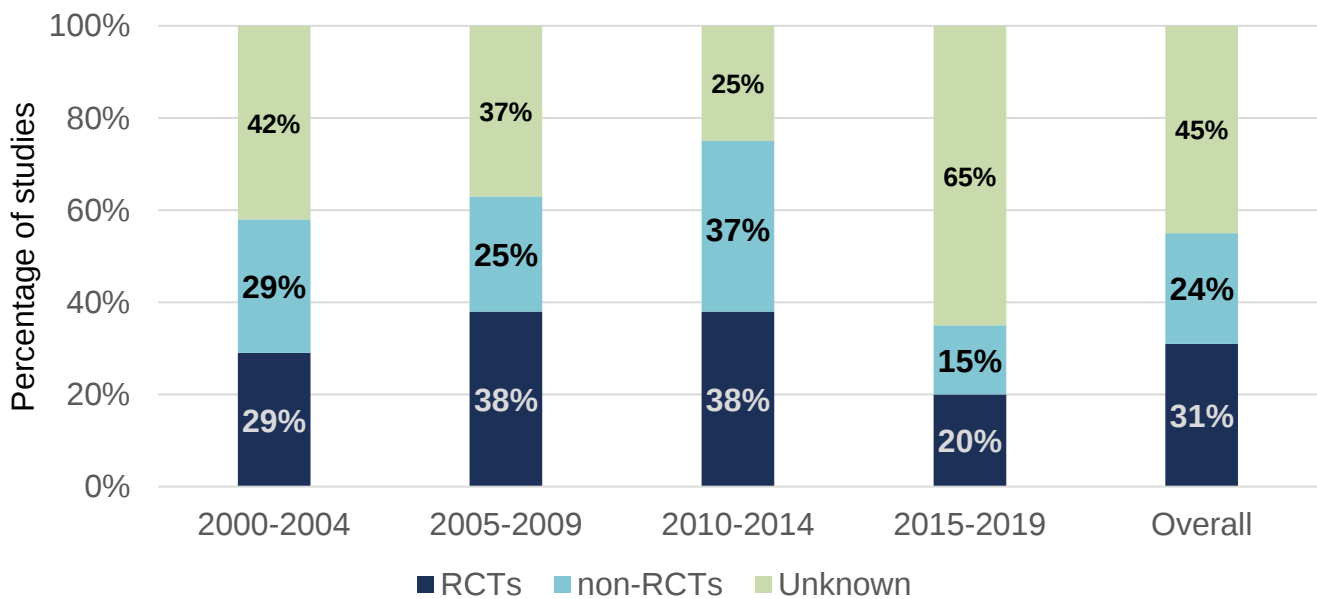
- Overall, 911 records were selected as relevant, which represent 0.3% of all studies submitted to the database.
- Of the retrieved studies a total number of 390 interventional trials were selected including 212, 118, 14 and 46 phase 1/2, 2, 2/3 and 3 trials, respectively. (Figure 1)

Figure 1. Flowcharts of gene therapy trials identified from CT database



- The overall proportion of randomised controlled trials (RCTs) and non-RCTs were 31% and 25% respectively. The allocation methods for 45% trials was not reported. The percentages of different allocation methods were relatively constant across 5-year periods analysed between 2000 and 2014, while allocation was not described for majority of studies registered between 2015 and 2019 (Figure 2).

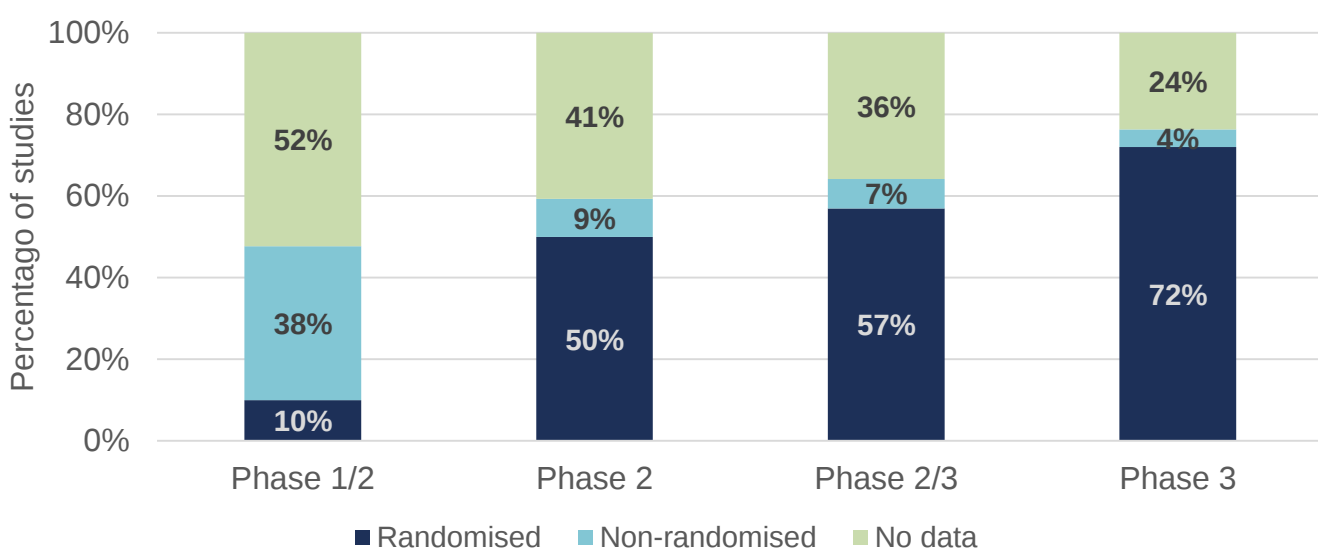
Figure 2. The allocation methods of included clinical trials between 2000- 2015



RCTs

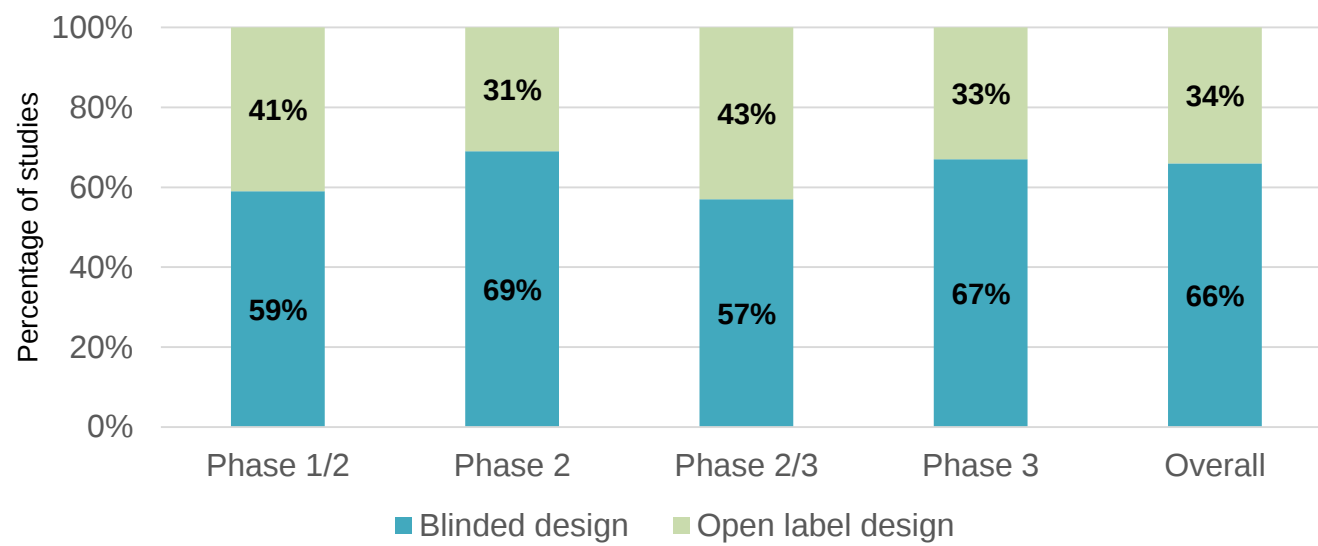
- Higher study phase was associated with a higher proportion of RCTs: 10%, 50%, 57%, and 72% for phase 1/2, 2, 2/3 and phase 3 trials, respectively. (Figure 3)

Figure 3. The distribution of allocation according to study phase



- Overall, blinded allocation and open label allocation was reported for 66% and 34% of RCTs respectively. No apparent interaction between study phase and masking was found. (Figure 4)

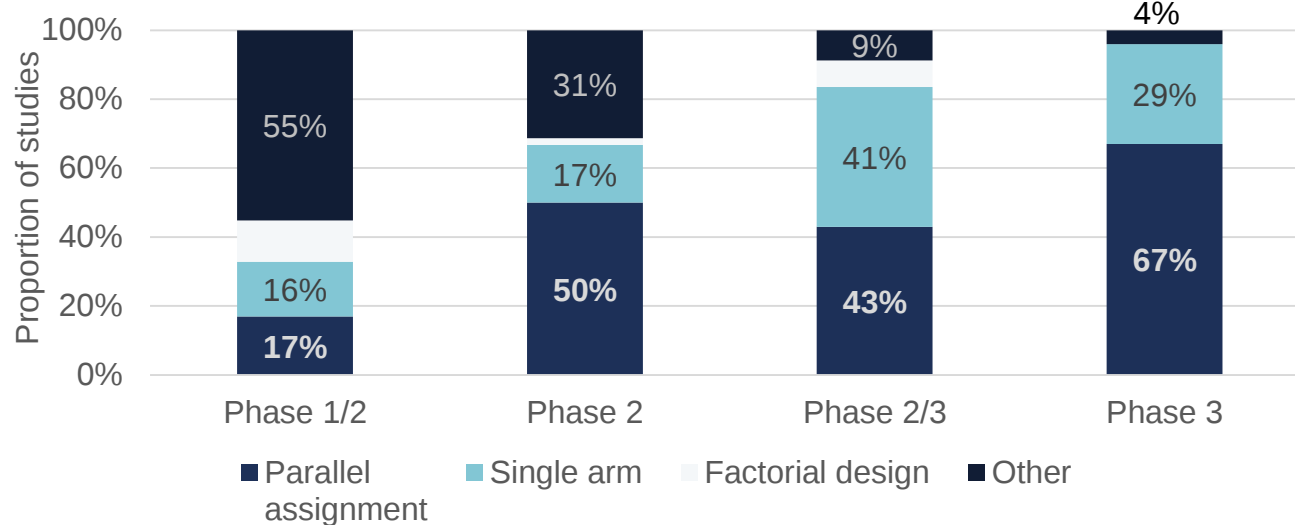
Figure 4. The distribution of masking methods among different phases



Non-RCTs

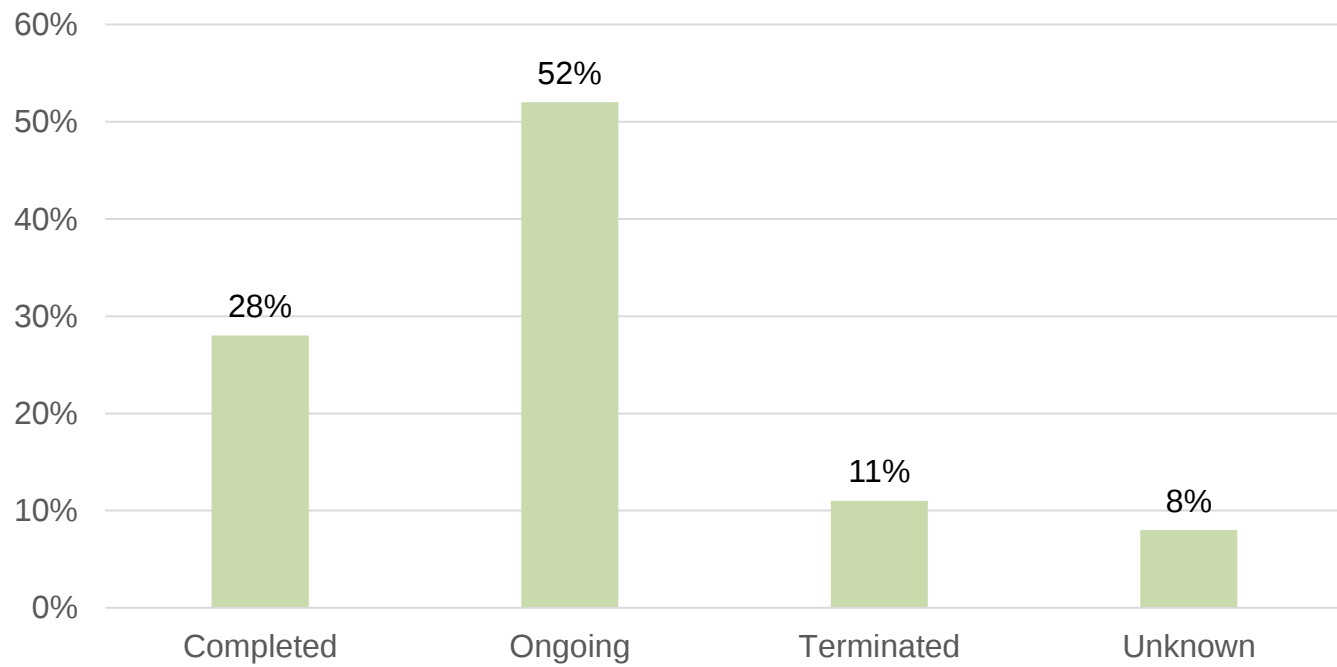
- The proportion of interventional non-RCT with a parallel assignment was 34% for all trials and 17%, 50%, 43% and 67% for phase 1/2, 2, 2/3 and phase 3 trials, respectively. (Figure 5)

Figure 5. The distribution of allocation method according to study phase



- Overall, 28%, 52% and 11% of trials were completed, ongoing or terminated, with no apparent interaction between status and study phase. The status was unknown for 8% of studies. (Figure 6)

Figure 6. Study status of included trials



CONCLUSIONS

- The overall number of advanced phase GT clinical trials is limited, although available evidence comprise of relatively high proportion of blinded RCTs and comparative non-RCT studies.
- A deeper assessment of the methodological credibility of advanced GT trials is required, including evaluation of the appropriateness of comparator selections, relevance of primary outcomes and sample sizes.
- CT.gov is a valuable source of data and it is good to trace the research development.

REFERENCES

- <https://clinicaltrials.gov/ct2/about-site/background>
- https://aact.ctti-clinicaltrials.org/pipe_files
- R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.