

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 provide opportunity to treat medical conditions, for which the available interventions are ineffective, or no intervention exist.
- CT records were explored to monitor the recent development of emerging gene therapies.

OBJECTIVE

The objective of this study was to characterise methodological design and distribution of indications among clinical trials for gene therapies (GTs).

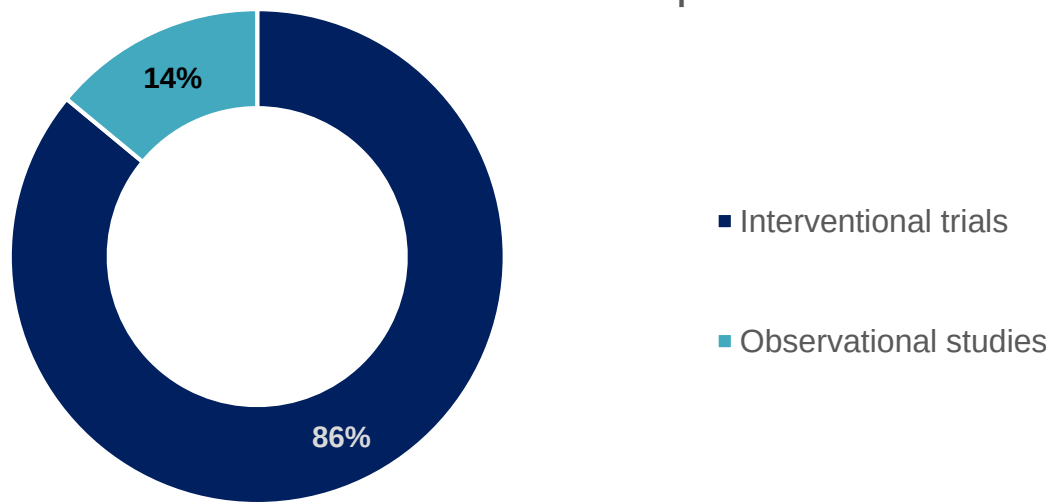
METHODS

- 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).
- The database mining was performed using Creativ-Ceutical in-house search engine written in R language. [3]
- CT database was searched for trials with at least one occurrence of keyword phrases: "gene therapy", "gene transfer" or "AAV" (adeno-associated vectors).
- The search was carried out for records in the database tables containing information about: trial keywords, title, summary, description, interventions, design, outcomes and participant flow.
- Identified data related to title, study description, study design, presumed and actual study timeframes, inclusion/exclusion criteria, enrolment, health condition, intervention applied, the outcomes and the results reported were transferred to Excel tables for further analysis.
- A descriptive analysis was conducted to summarise the distribution of 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

- The overall number of 911 records were retrieved, of which 780 were interventional trials (86%) and 131 were observational studies (14%). (Figure 1)

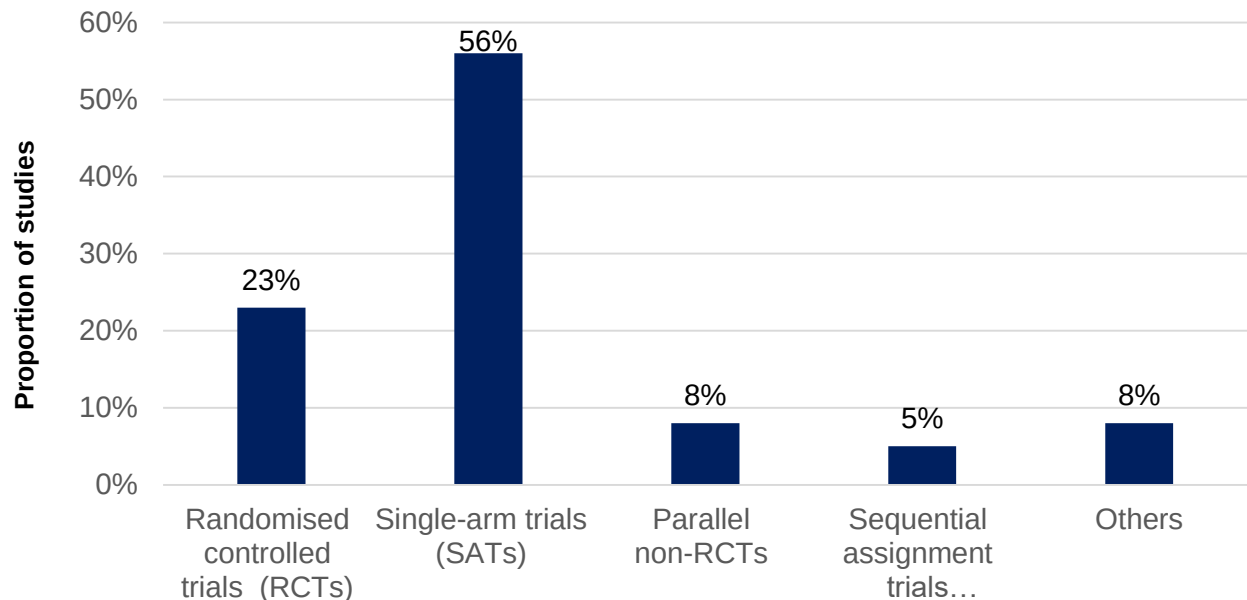
Figure 1 Characteristics of clinical trials for gene therapies



Methodology of interventional trials

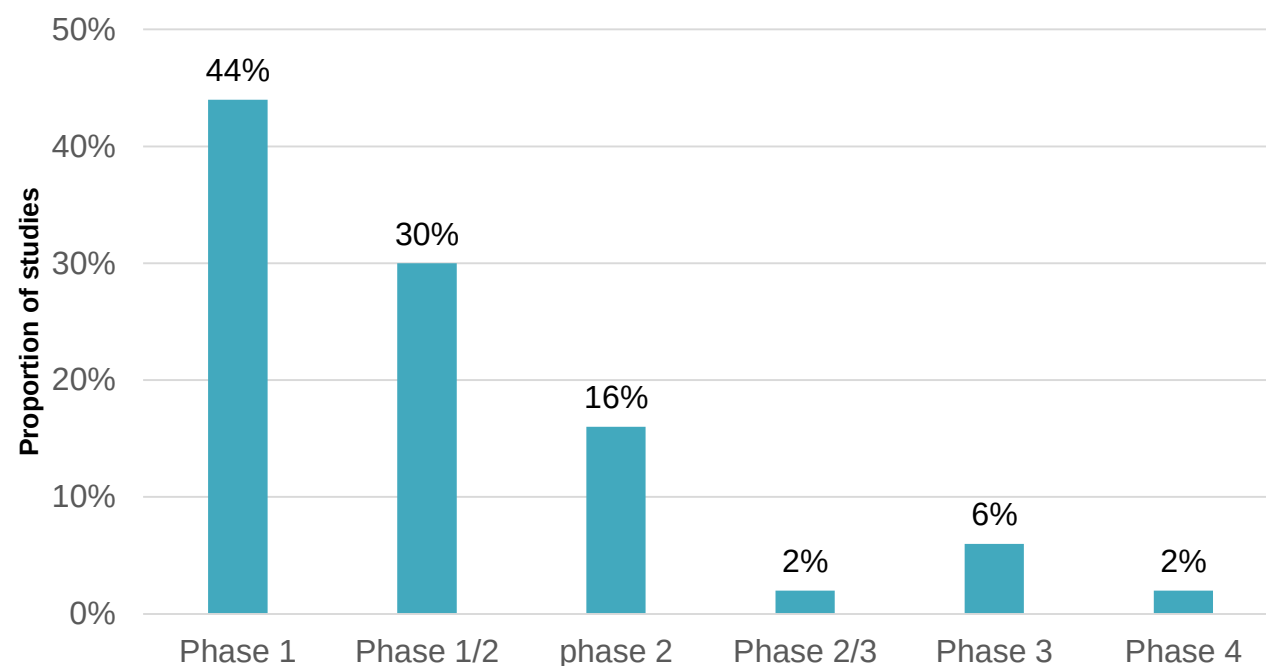
- Of the interventional studies, 23% were described as randomised controlled trials (RCTs), of which 68% were blinded and 32% were open label trials.
- The remaining interventional trials adopted single-arm (SAT) (56%), parallel (8%), sequential (5%) or factorial (<1%) assignment strategy.
- The information regarding patients' assignment was not provided for remaining records (7%) (Figure 2).

Figure 2. The design methods among interventional trials



- Of the interventional trials, 44%, 30%, 16%, 2%, 6% and 2% were phase 1, 1/2, 2, 2/3, 3 and phase 4 studies, respectively. (Figure 3)

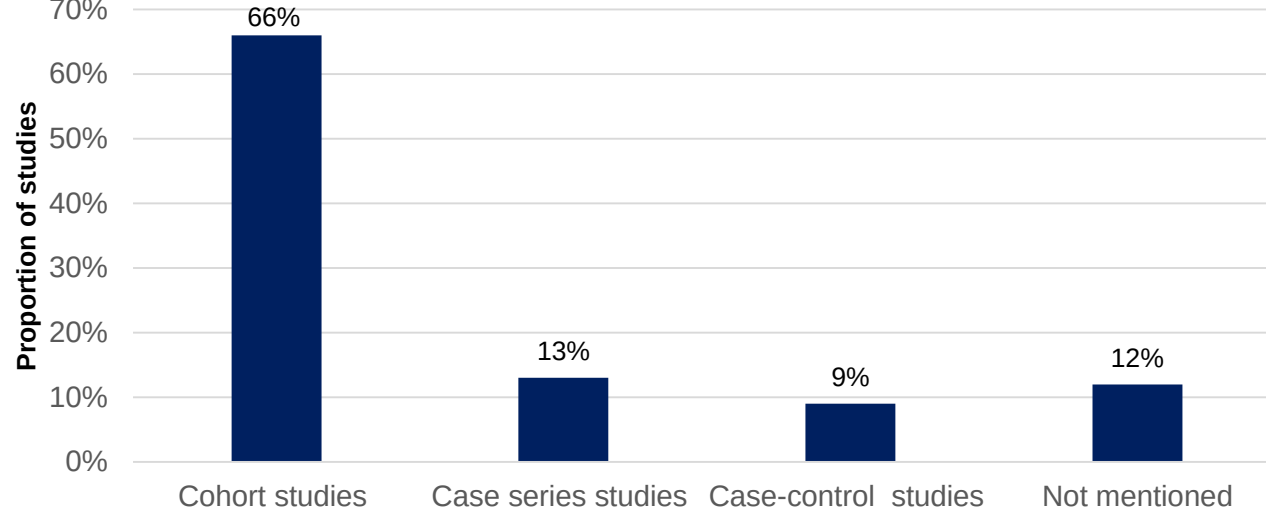
Figure 3. The distribution of study phases among interventional trials



Methodology of observational studies

- Identified 131 observational evidence were cohort (66%), case series (13%), and case-control (9%) studies. The remaining 12% studies were without methodological description.(Figure 4)

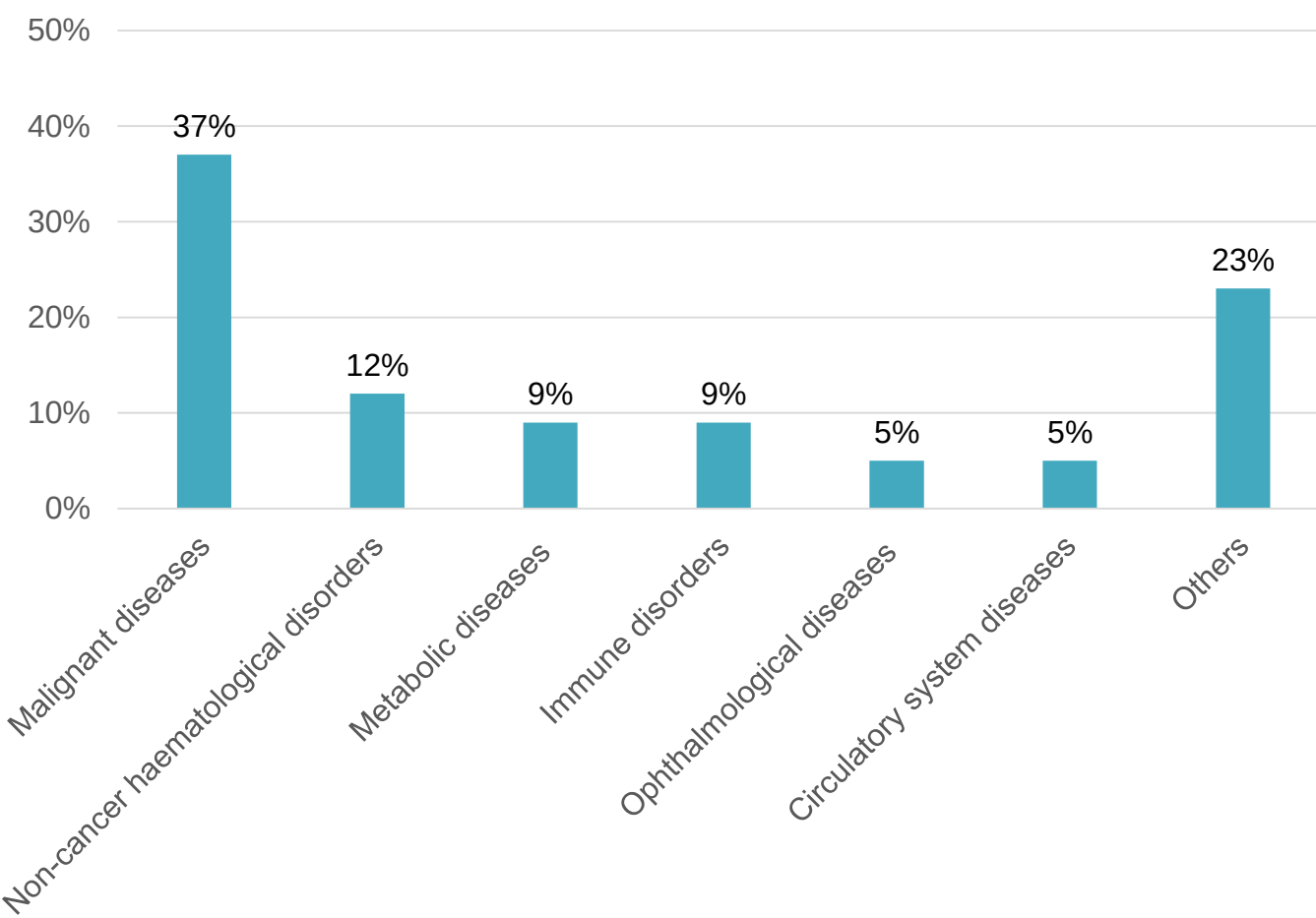
Figure 4. The design methods among observational trials



Primary outcomes and target population

- A total of 70% of all studies assess clinical efficacy, of which 52% adopted patient relevant primary endpoints, and 48% a surrogate end point.
- A total of 37% studies related to malignant diseases, 2/3 solid tumours, followed by non-cancer haematological disorders (12%), metabolic diseases (9%), immune disorders (9%), ophthalmological diseases (5%) and diseases of circulatory system (5%). (Figure 5)

Figure 5. The distribution of diseases among the all identified trials



CONCLUSIONS

- The studies assessing gene therapies are predominantly interventional trials targeting primarily oncology indication
- The methodological credibility of the gene therapy clinical trials is limited:
 - GT trials are predominantly single-arm studies,
 - 44% of interventional studies were early phase 1 trials,
 - Half of the studies assessed surrogate outcomes.
- This will pose a challenge for future HTA assessment.
- New guidelines for assessing single-arm trials using surrogate end point are needed.

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/>.

