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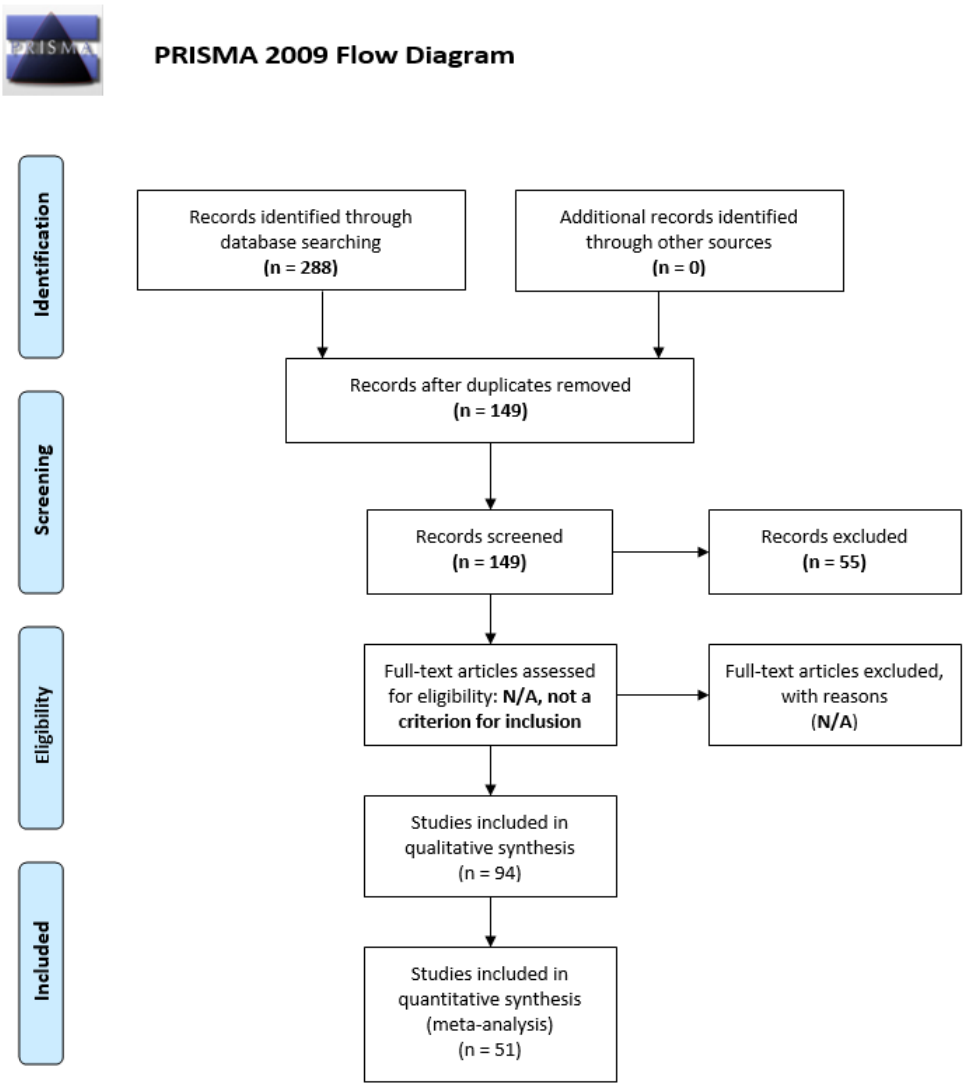
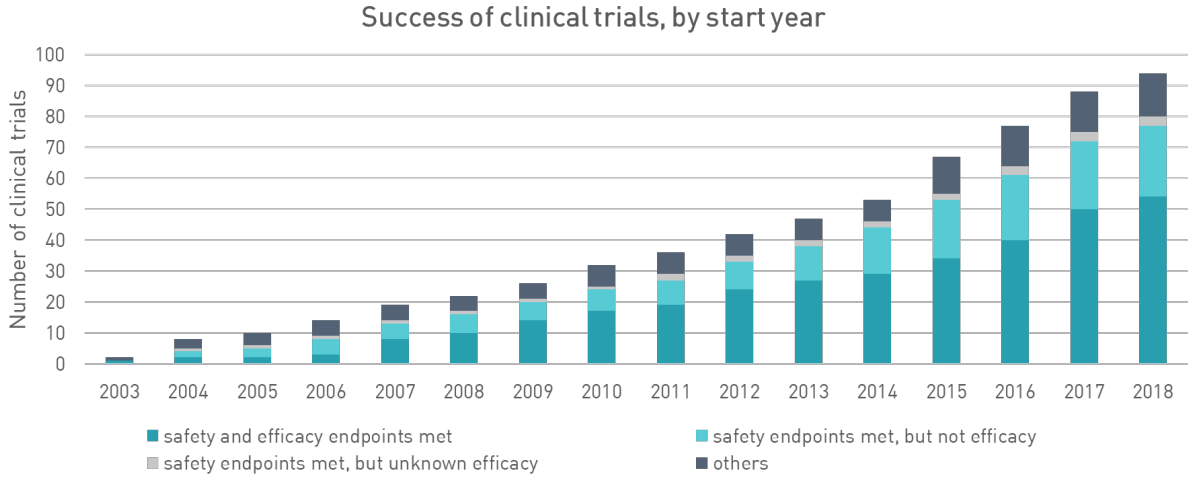
Supplementary information

The clinical landscape for AAV gene therapies

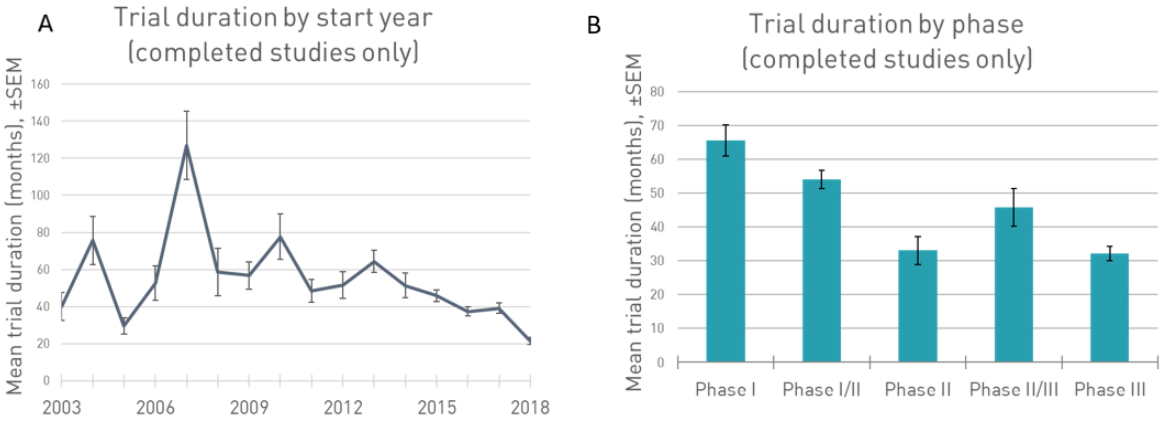
In the format provided by the authors



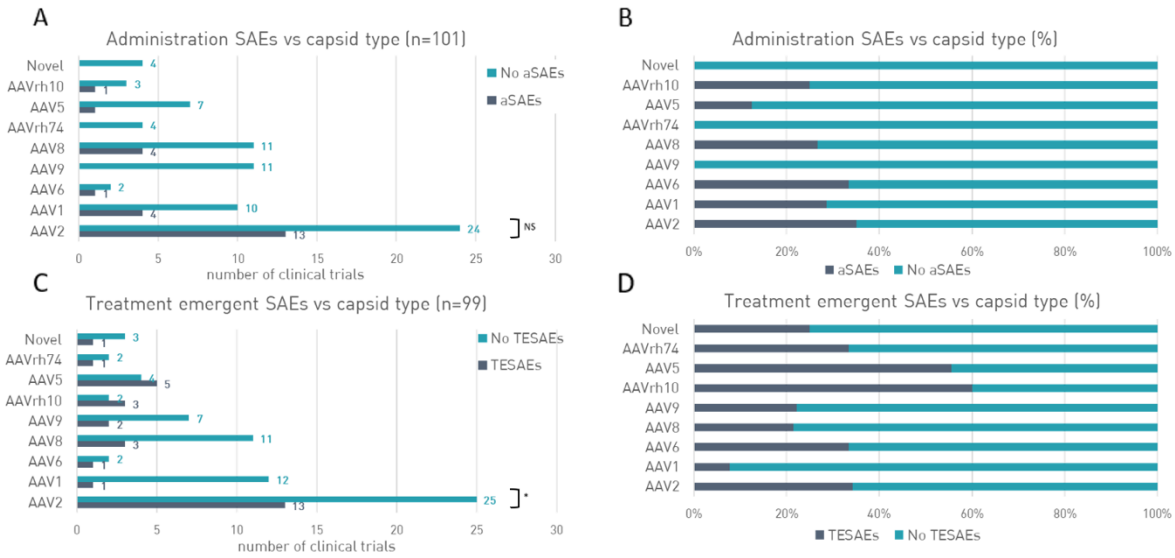
Supplementary Fig. 1 | PRISMA flow diagram. The systematic review of the landscape of clinical trials of AAV-based gene therapies was performed according to the 2009 PRISMA guidance, which is used for reporting of meta-analyses of randomized controlled trials (Moher et al., *PLoS Med* 6(7): e10000097, 2019). The flow diagram describes a four-phase flow analysis of clinical trials of AAV-based gene therapies. A total of 288 trials were found registered with the US FDA database (www.clinicaltrials.gov) or the EUDRA CT (https://eudract.ema.europa.eu/) as of 01.01.2020 inclusion cut-off date. Of these, 149 were identified as unique clinical trials after the removal of reporting, geographical and multi-centre duplicates (June 2003–July 2020). Of these, 55 were excluded from analysis as they did not report efficacy or safety data; 94 were included into the qualitative synthesis as well as the quantitative analysis on safety. A total of 51 trials reported both safety and at least interim efficacy data. These were included into the quantitative synthesis for the purposes of establishing efficacy rates, clinical trial phase transition and success probabilities.



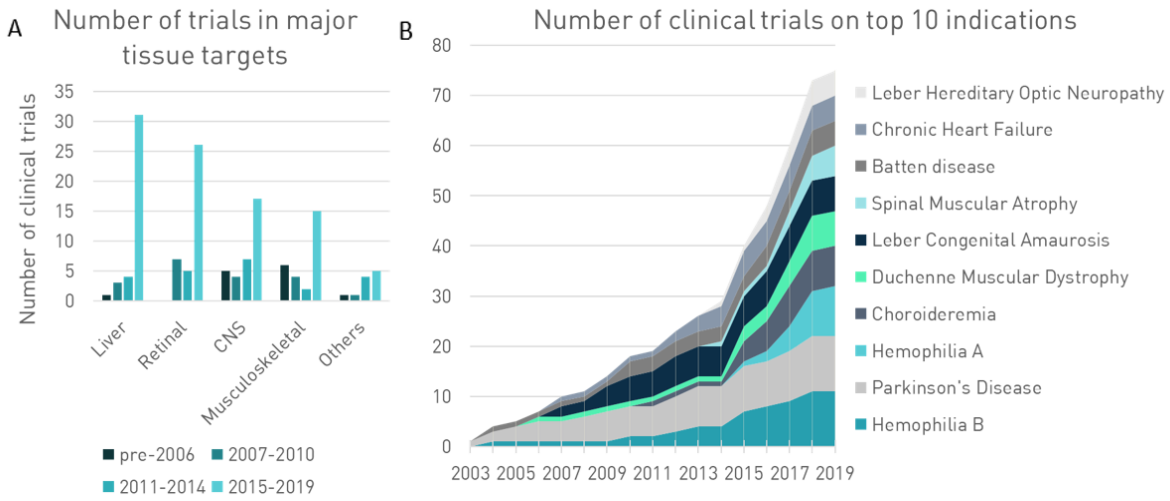
Supplementary Fig. 2 | Trial outcomes by year, cumulative.



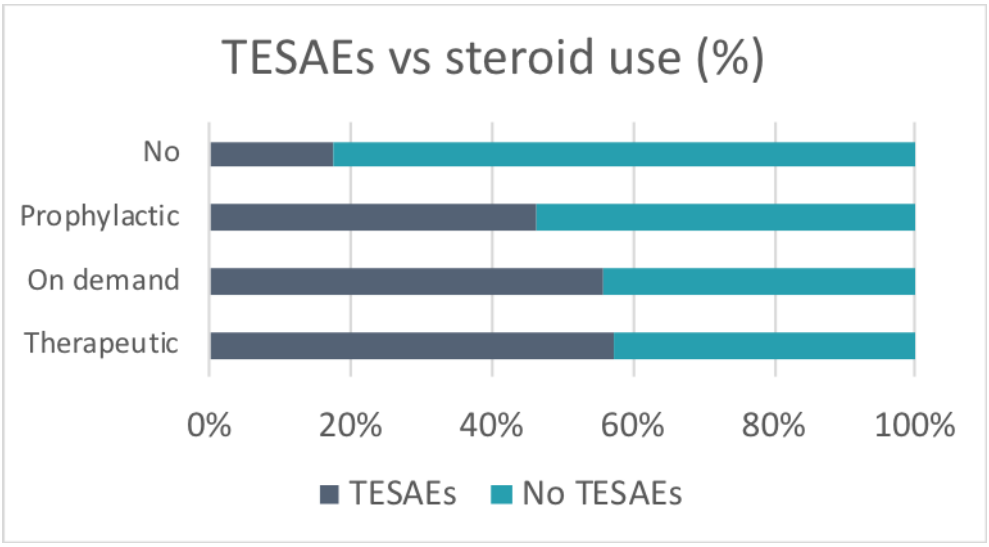
Supplementary Fig. 3 | Trial duration by start year and phase, 2003–2019. A | Mean trial duration ± SEM reported by year of initiation. **B** | Mean trial duration ± SEM reported by trial phase (n = 51 completed studies in both). Trial duration calculated as the difference between the date of primary completion and the date of initiation, in months.



Supplementary Fig. 4 | **Administration-related and treatment-emergent SAEs by capsid type**. SAEs reported by the investigators as those occurring within 28 days of administration were treated as administration-related in this analysis. We chose the 28-day cut-off period based on three observations: (i) this being the most frequent cut-off reported in the trial designs for AAV gene therapy clinical trials, as well as being well-established in the related trials of recombinant adenoviral vaccines; (ii) a typical transgene taking ~28 days post-administration of the AAV to reach full expression, as reported by multiple clinical studies included in this meta-analysis, thus making transgene-related AEs impossible to separate from administration-related after ~28 days; and (iii) the maturation of a *de novo* immune response to the capsid or the transgene reported to take a ~28 day time period, thus making any immune-related AEs impossible to separate from the administration-related after this time-period. Conversely, most clinical trial protocols reviewed for this meta-analysis assume that most administration-related AEs resolve within 28 days of the administration itself, therefore, most AEs occurring or persisting post that date are treatment-emergent. Capsids LK200, AAVHSC15, SPK100, AAVhu37 were pooled as 'Novel'. **A** | Administration-related SAEs by capsid type, number of trials with and without SAEs, n = 101 trial reporting both capsid type and administration safety data. **B** | Administration-related SAEs by capsid type, percentage of trials with and without SAEs, n = 101 trial reporting both capsid type and administration safety data. **C** | Treatment-emergent SAEs by capsid type, number of trials with and without SAEs, n = 99 trial reporting both capsid type and treatment-emergent safety data. **D** | Treatment-emergent SAEs by capsid type, percentage of trials with and without SAEs, n = 99 trial reporting both capsid type and treatment-emergent safety data. For the two most used capsid types, AAV2 and AAV1, there was no significant difference (Z-test for two proportions) in administration-related SAEs (p = 0.32, ns), and a borderline significant difference in treatment-emergent SAEs (p = 0.035).



Supplementary Fig. 5 | Tissue targets and indications. A | Number of trials in major tissue targets, by time periods. **B** | Cumulative number of clinical trials on top 10 most pursued indications (n = 75 out of 149 trials).



Supplementary Fig. 6 | Treatment-emergent SAEs with or without steroids. Steroid use is poorly reported in clinical trial protocols and publications. Trials disclosing steroid use (n = 46) were classified in the following way. Trials that reported no steroid use as 'No'; trials incorporating prophylaxis in all patients by default as 'prophylactic'; trials incorporating use of steroids on demand or at investigator discretion in the protocol as 'on demand'; trials which did not incorporate the use of steroids in their protocol, but indicated that certain AEs resolved 'with use of steroids' as 'therapeutic'. All differences were not significant.

Additional information on figures included in the main article

Fig. 1 | Overview of clinical trials involving gene therapies using adeno-associated viral vectors (AAVs). **a** | Number of clinical trials initiated per year. Date of initiation as reported to the relevant database (www.clinicaltrials.gov or EudraCT). Note that the date of initiation can be significantly different from the date of the first registration of the trial on either of the platforms. The trials were classified as academic (if the trial sponsor is an academic institution or a healthcare institution) or commercial (if the trial sponsor is a corporate entity). For the avoidance of doubt, where INDs sponsored by research institutions were financed by corporate supporters through research agreements or otherwise, the trials were classified as academic. **b** | Number of clinical trials by phase. Not shown: the number of phase I trials not incorporating an efficacy endpoint (thus not phase I/II trials) is decreasing over time. **c, d** | Number of clinical trials with different capsids and promoters, respectively. Capsids LK200, AAVHSC15, SPK100 and AAVhu37 were pooled as 'Novel'. The time periods were picked as follows: any data available prior to 2007 mandatory trial registration; 2007–2010, trials prior to the first trial reporting significant evidence of biological transgene activity with AAV gene therapy in haemophilia (see *Mol. Ther.* **19**, 876–885; 2011; *N. Engl. J. Med.* **365**, 2357–2365; 2011); after that, at regular intervals.

Fig. 2 | Administration-related and treatment-emergent SAEs by route of administration. For classification of SAEs and reporting analysis, see Supplementary Fig. 4. **a** | Administration-related SAEs by route of administration, *n* of trials with and without SAEs, *n* = 100 trials reporting both route of administration and administration safety data. **b** | Treatment-emergent SAEs by route of administration, *n* of trials with and without SAEs, *n* = 100 trials reporting both route of administration and treatment-emergent safety data. For the two most used routes of administration, intravenous and subretinal, there was borderline significant difference in administration-related SAEs ($p = 0.039$), and no significant difference in treatment-emergent SAEs ($p = 0.49$, not significant).