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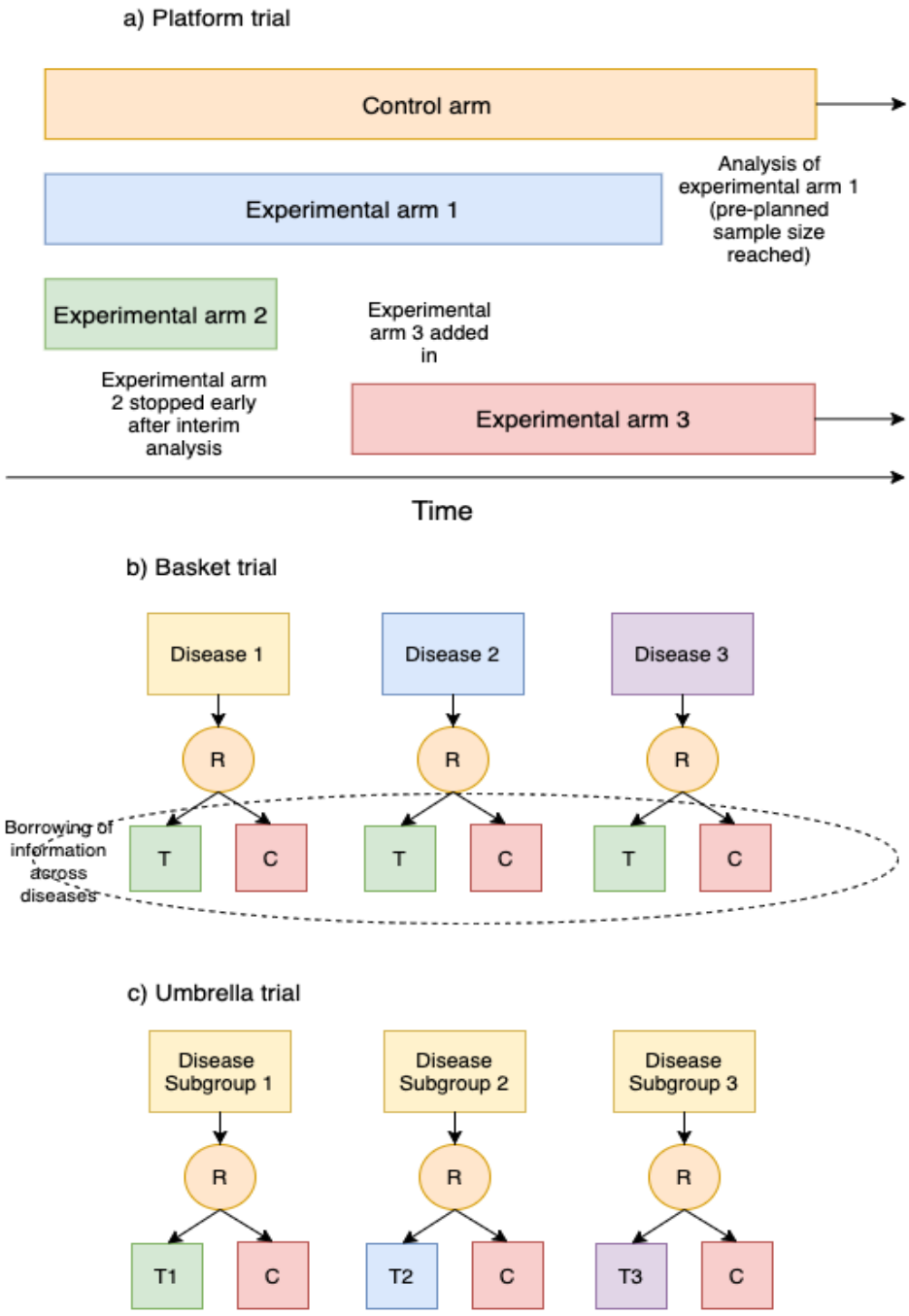
Supplementary information

The potential of innovative trial design for efficiently evaluating repurposed drugs

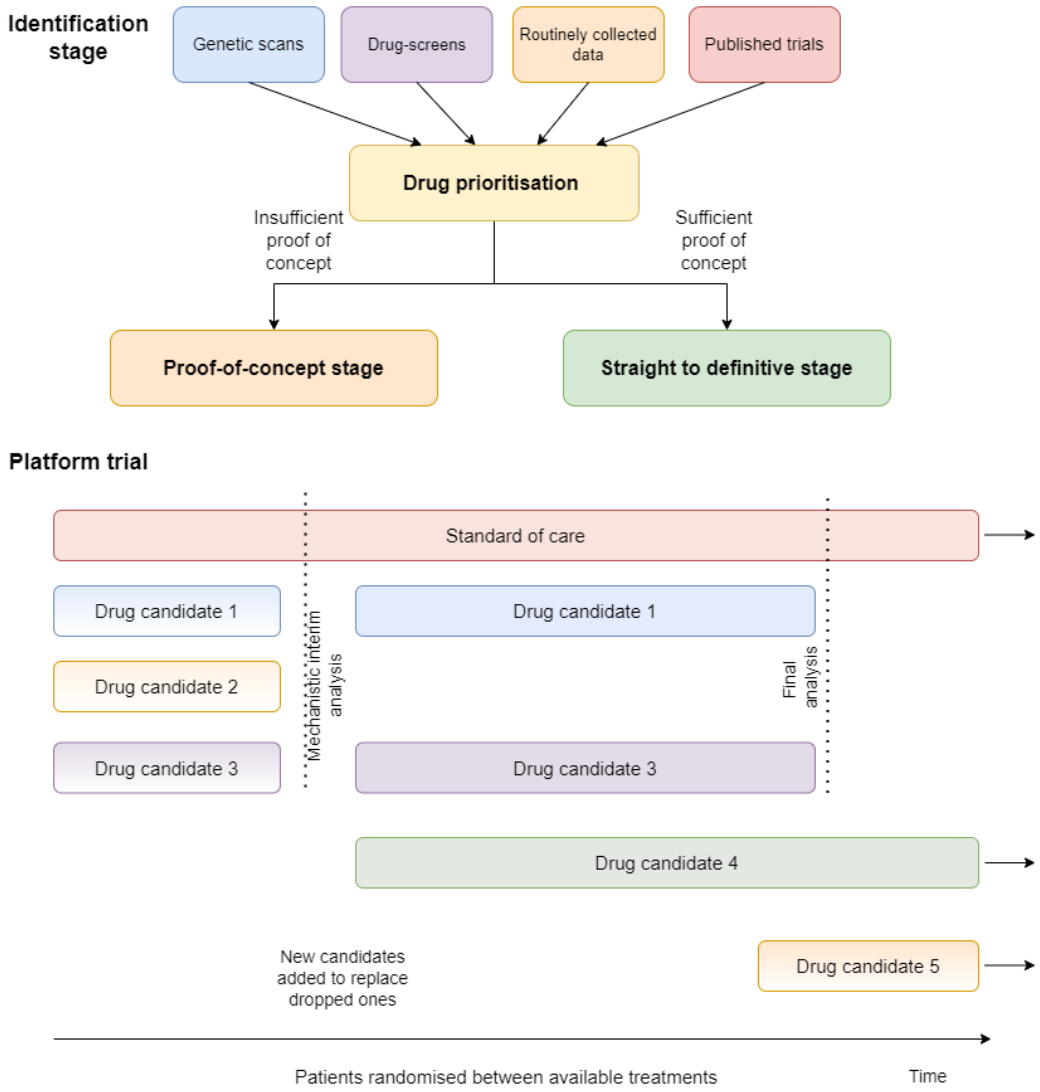
In the format provided by the authors



Supplementary Figure 1 | Overview of master protocols. See Supplementary Table 1 for a description of the types of protocol and their relevance for drug repurposing.

Supplementary Table 1 | **Master protocols and how they could be used for improving repurposing**

Master protocol type	**Description**
Platform trials (Supplementary Figure 1a)	Platform trials allow assessing multiple experimental arms with a shared control group and are a highly efficient way to evaluate a (potentially increasing) set of promising treatments over time. Existing large confirmatory platforms have evaluated repurposed treatments for COVID-19[1,2] and for prostate cancer[3]. Platform trials would also be an efficient way to conduct small proof-of-concept trials as well and would avoid some of the statistical issues that are present in confirmatory platform trials[4]. Adaptive designs[5] would allow early stopping of treatments for lack of benefit (i.e. where the pre-trial promise did not translate into patients), as long as an endpoint could be used that is observed relatively quickly compared to the length of recruitment[6].
Basket trials (Supplementary Figure 1b)	Basket trials allow the simultaneous assessment of an approved drug for multiple conditions in an efficient way. They have been traditionally been used for testing targeted treatments in oncology[7].Where a common endpoint can be specified (e.g. a common mechanistic endpoint or symptom-related clinical endpoint), advanced statistical analysis approaches can be used to borrow information to improve power[8]. Even when common endpoints cannot be specified, conducting basket trials would provide operational efficiencies compared to conducting separate trials.
Umbrella trials (Supplementary Figure 1c)	Umbrella trials allow testing multiple treatments in subgroups of a (single) heterogeneous condition where different treatments act upon different mechanisms and/or tackle different symptoms. Trial participants may be stratified into different subgroups that are expected to benefit from different repurposed drugs.



Supplementary Figure 2 | Proposed repurposing platform. Drug candidates 1-3 are judged as warranting a proof-of-concept evaluation, whereas the evidence for drug candidate 4 is sufficiently strong that it proceeds directly to the definitive stage. Drug candidate 2 does not demonstrate sufficient proof-of-concept to continue to the definitive stage, and drug candidate 5 is moved into proof-of-concept evaluation to replace it.

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