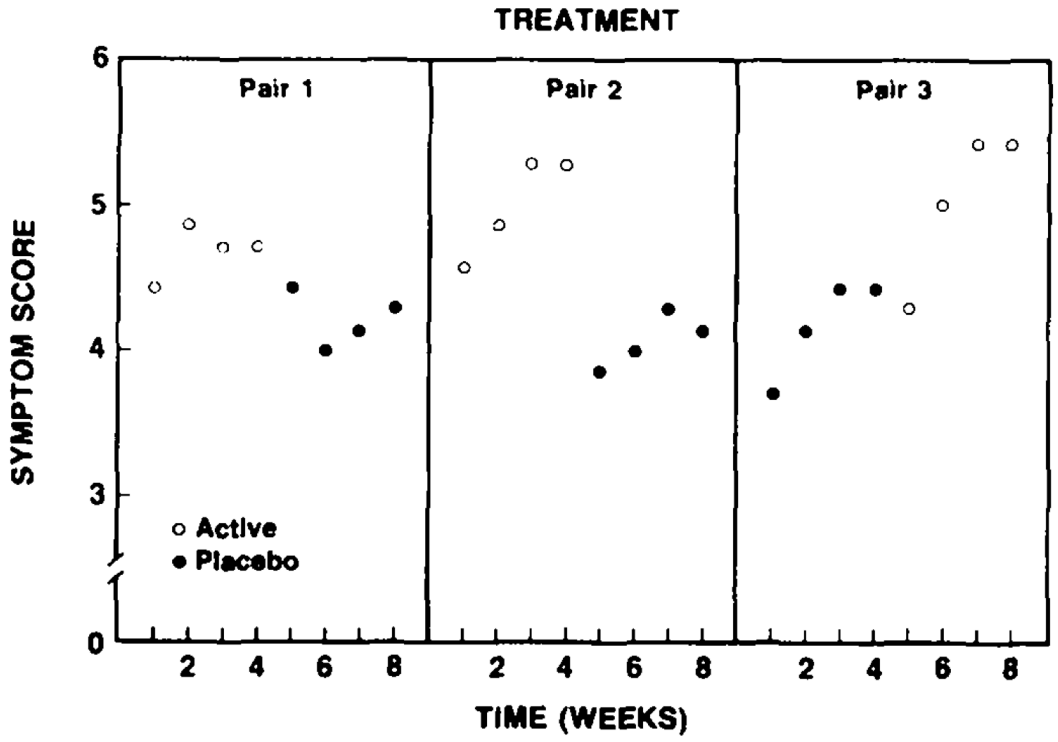
Table 1
Comparison of case studies to N-of-1 trials.

Study design	Time orientation	Number of measurements	Randomized	Blinded	Control	Bias
Case study	Often retrospective	Limited; based on clinical need	No	No	Possibly	Yes
N-of-1 trial	Always prospective	Many	Yes	Yes	Yes	Likely

N of 1 trials [randomized trials in individual subjects (N of 1 RCTs)]

- At an early stage of drug development
- In appropriate conditions N of 1 RCTs can be used to define the rapidity with which a drug begins and ceases its clinical action, the likely range of the optimal drug dose, and the optimal outcomes on which subsequent trials should focus
- Relation with crossover trial: N of 1 trials attempt to establish effects in an individual, crossover trials attempt to establish effects in a group. One may analyze a series of N of 1 trials with a similar design as a multiple crossover trial ;
- N of 1 RCTs are unlikely to be useful when major outcomes that occur over the long term (including death, or major morbidity such as stroke) are the end points of interest.



The major limitation of N of 1 RCTs is that they are most appropriate if the condition under study is chronic and relatively stable, for drugs which manifest an effect on a clinically important treatment target within days to several weeks and whose effect is reversed over a similar time period when withdrawn.

Table 1 Issues and Opportunities Using *N* of 1 Trials in Drug Development

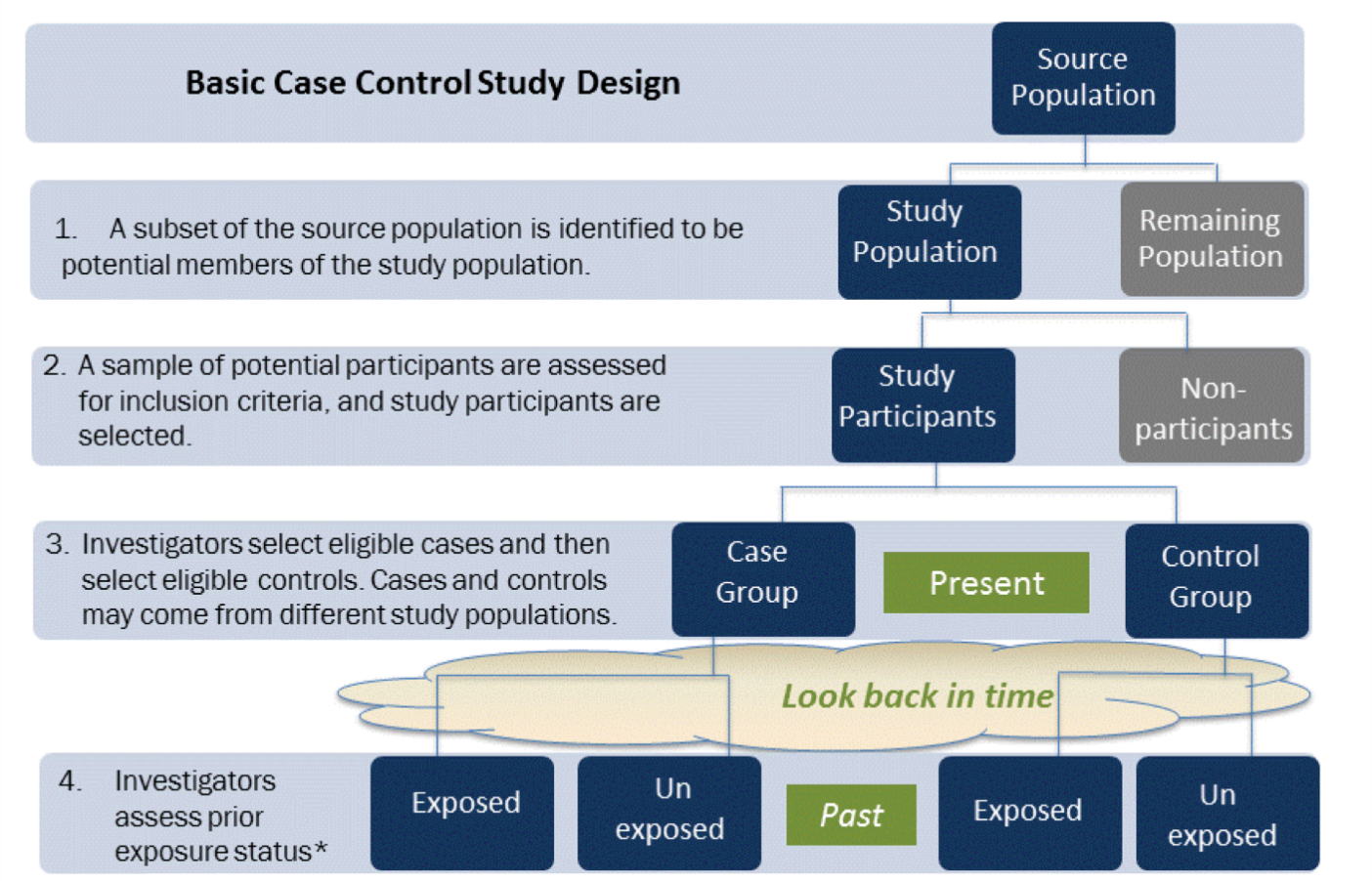
1. The role of unmasked trials of medication
   Does a negative unmasked trial exclude benefit?
2. Determining the rapidity of onset of drug action
   How quickly does the drug begin to act, and cease acting?
3. Optimizing dose
   What is the "best" dose? Does it differ between patients?
4. Measurement of outcome
   What outcomes are most influenced by the new drug?
5. Study design and statistical analysis
   What designs and analytic tools are available for planning *N* of 1 RCTs, and for evaluating their results?
6. Interpreting the results of *N* of 1 RCTs
   What a priori criteria should be established for classifying a trial as definitively positive, definitively negative, or indefinite?
7. Assessing potential drug impact
   Will the drug have a significant impact on the disease?
8. Predicting response
   Are there features that discriminate between responders and nonresponders?

Table 2
Determination that an N-of-1 trial is feasible.

Question	Determination	Example
Is treatment efficacy questionable?	If it is clear to the patient and provider that a treatment does or does not work, then an N-of-1 trial is unnecessary.	After dramatic decrease in seizure frequency following the initiation of a new medication, an N-of-1 trial would be unnecessary to determine if therapy should be continued.
Is treatment for a chronic condition?	Given the resources needed to conduct an N-of-1 trial, they are only recommended for chronic conditions.	An N-of-1 trial for a single case of status epilepticus is not feasible.
Is there a rapid treatment onset and offset?	N-of-1 trials are only reasonable for therapies with quick onset and offset.	An N-of-1 trial with carbamazepine may not be feasible. Levetiracetam is an appropriate therapy for an N-of-1 trial.
Can the outcome be measured in a reasonable amount of time?	When taking the duration of a therapeutic trial and the number of trials, it is suggested to try to keep the N-of-1 trial to less than 12 weeks. However, patient willingness to complete the trial will factor into how long the trial can last.	For a patient who averages one seizure per week, a minimum of three weeks is needed to measure therapy efficacy. If an additional week is needed to washout and transfer to a new therapy, this N-of-1 trial would take upwards of 6 months to complete. This may not be considered reasonable by many patients.
Can the pharmacy department assist?	Pharmacy departments can often serve as the removed nonblinded individual.	Pharmacy departments can perform the randomization and prepare the therapy and placebo or control to maintain patient and provider blinding.
Is the patient interested in an N-of-1 trial?	Shared-decision making with a cognitively intact patient is essential for patient selection in an N-of-1 trial.	It is unethical to give a placebo or control therapy to a patient who has not undergone informed consent. Additionally, if a patient is uninterested in the N-of-1 trial, they will be unlikely to complete the required data collection.

Case control study:

- identify factors that may contribute to a medical condition by comparing subjects who have the condition with patients who do not have the condition but are otherwise similar
- require fewer resources but provide less evidence for causal inference than a RCT
- Choose control group according to the characteristics of case group (not randomized can we get causal relation?)
- Unlike cohort or cross-sectional studies, subjects in case-control studies are selected because they have the health outcome of interest (cases). Controls, persons who are free of the health outcome under study, are randomly selected from the population out of which the cases arose. The case-control study aims to achieve the same goals (comparison of exposed and unexposed) as a cohort study but does so more efficiently, by the use of sampling.



Reference books for Causal Case Control Study:

https://escholarship.org/uc/item/37z0371r

https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-021-01484-7

chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.diva-portal.org/smash/get/diva2:757008/FULLTEXT01.pdf

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