

Single Subject (N-of-1) Research Design, Data Processing, and Personal Science

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Background

Single subject research design, also known as N-of-1 research, is a scientific method in which an individual person serves as the research subject. We treat “N-of-1” and “single subject” as synonyms encompassing all scientific practice which focuses on observations made about a single person. Other names for similar and overlapping approaches include: single case experiments [1–3] single case research [4, 5], single case designs [6], and single patient trials [7]. Some authors distinguish between single subject research in general, which may be descriptive and exploratory in character, and single subject experiments that are prospectively planned and use formal methods such as randomization, blinding, or crossover comparisons. Here, we use N-of-1 and single subject research as synonymous, high level general terms for research focused on an individual rather than a group.

N-of-1 research is common in applied fields of psychology, education, and human behavior where it has benefited from extensive methodical research and practical guidance for practitioners [8, 9]. However, over a half-century of study and advocacy, including pioneering publications by Guyatt et al., Larson et al., Mahon et al.,

and others, have failed to establish single subject science as central to research and practice in medicine [10–13]. A systematic review of 122 eligible N-of-1 studies published between 1985 and 2013 showed wide variation in methodology and reporting, reducing the power of these studies to influence practice [14]. Researchers advocating N-of-1 techniques have noted that the practical obstacles to design, conduct, analyze and apply the results for single subjects have simply been too high [15, 16].

Nevertheless the rise of personalized medicine and patient-centered research create new opportunities for using N-of-1 methods [17, 18]. Recent key publications include an extensive and comprehensive user guide for the design and implementation of N-of-1 trials [19], an update of the standard (CONSORT) for reporting N-of-1 trials [20, 21], and a special issue of the *Journal of Clinical Epidemiology* devoted to individual patients as the primary source and target of clinical research [22].

General public interest in gathering data about health is also growing. A Pew Internet study conducted in 2013 found that 1 in 5 Americans use some form of technology to track their health [23]. In 2016, the number of consumers in the United States who use mobile health apps increased from 16 percent in 2014 to 33 percent and the number of consumers who use health wearables increased from 9 percent to 21 percent [24]. According to data from the International Data Corporation (IDC), 104.3 million wearable devices were shipped in 2016, a number that is likely to be almost doubled by 2021 [25]. The increasing availability of home blood testing kits, wearable glucose monitors, and heart rate monitors, among other consumer

health tools and services, suggest a large scale transformation of the measurement context for N-of-1 research. The combination of increased public interest and reliable measurement technologies broadly available may reduce the barriers to application of N-of-1 methodology [16, 26].

These consumer technologies have already attracted research attention. For instance, activity trackers made by Fitbit, Inc, have been deployed as instrumentation in over 450 public scientific studies [27]. Of course, application of wearables for clinical or research practice requires the technology to be valid and reliable. Research has found considerable variation of accuracy in different consumer wearables, including activity trackers [28–30], sleep trackers [31, 32], and wrist worn heart rate monitors [33, 34]. Despite this variation, there have been some notable successes. For instance, in an innovative two year study published in 2017, Li et al. demonstrated that measurement of heart rate and skin temperature using consumer wearables could predict inflammatory response as revealed by laboratory blood work showing elevated hs-CRP and onset of symptoms [35]. In presenting the articles in this focus theme, we aim to encourage attention to single subject research from both scholars and researchers in health and biomedical informatics who may play a key role in advancing its practical methods and resolving doubts about its power and validity.

This focus theme

We present three examples of well-designed N-of-1 studies, performed by scientists on independent individual research

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subjects. Bartels-Velthuis et al. [36] present a replicated single-subject design that was used to test the effect of a heart rate variability biofeedback relief program on depression. They show that a stress reduction program is beneficial in some psychological domains and for some patients. Dori Rosenberg et al. [37] studied the application of N-of-1 experiments to test the efficacy of inactivity alert features in fitness trackers to increase breaks from sitting in older adults. Their work shows that inactivity alert features within commercially available devices are efficacious for promoting modest improvements in breaks from sitting among older adults with obesity. Victor Lee et al. [38] describe their multi-year comparison of discovered regularities in blood glucose readings across two data collection approaches used for a child with type 1 diabetes. Their work shows how family routine and school schedules may inadvertently introduce blind spots in data, even when it's collected and recorded systematically. This is a retrospective study in which the authors have also taken heart-warming care as parents. The child is a co-author for its participatory role which resonates well with the next type of contributions.

In this focus theme we also introduce a specific type of single subject research: the self-directed N-of-1 study. In a self-directed N-of-1 study, the subject of the research is also the primary investigator. This type of N-of-1 study is of special interest today because the increasing popularity of consumer biosensing, software for data visualization and analysis, and web access to scientific literature and peer support have made it possible for more people to carry out experimental and quasi-experimental projects using their own self-collected data.

Since self-directed N-of-1 studies are typically driven primarily by individual, often highly personal questions, rather than by the research agenda of an academic or clinical discipline, they require a different mode of presentation. Here, we present these types of articles under the name "personal science reports". Personal science reports are original, self-directed N-of-1 contributions carried out with sufficient empirical rigor to merit close attention from the professional research community. In

this focus theme, they were not peer-reviewed, but underwent editorial review by the issue editors and, where appropriate, outside readers with specialized knowledge. The goal of presenting these papers is not to offer research contributions to a particular scientific discipline but to highlight individual work that merits discussion.

This issue contains three personal science reports: Paul Cooper [39] presents his data from a personal project that aimed to test an activity tracker for a possible correlation of resting heart rate with life events, showing possible associations with a cold virus as well as with the strain of a turbulent period in his personal life; Smarr et al. [40] present a personal science report using emerging methods of tracking gut microbiome changes resulting from a colonoscopy, demonstrating that the gut microbiome can have major changes on a daily basis when the host system has a major insult to its environment; Krutko et al. [41] present the results of a long-term computerized self-quantification of mental performance, sensorimotor coordination and emotional state, showing a systemic age-related deterioration of mental performance in a period of nine years, circadian rhythms of work capability and psycho-emotional state, and annual rhythms of sensorimotor skills. In a hybrid contribution, Riggare et al. [42] present a paper that is both a peer-reviewed study and a personal science project, describing a placebo controlled study on the effects of nicotine on dyskinesia of one person with Parkinson's disease, suggesting that nicotine administered via e-cigarette may be a useful approach to ameliorating levodopa-induced dyskinesia in individual patients with Parkinson.

Finally, we present two studies that reflect on the concept of single subject research design and data processing. Hsueh et al. [43] analysed N-of-1 mHealth data in order to test whether nomothetic or ideographic approaches are superior in predicting daily exercise behaviors. They demonstrate that it is feasible to perform personalized exercise behavior prediction, mainly made possible by mobile health technology and machine learning analytics. Eric Daza [44] presents an advanced and extensive

paper on the counterfactual-based causal inference for N-of-1 time series. The paper aims at bridging the methodological gaps between risk-factor discovery and N-of-1 randomized trials. It shows that causal analysis of an individual's time series data can be facilitated by an N-of-1 randomized trial counterfactual framework. For inference to be valid, the veracity of certain key assumptions must be assessed critically, and the hypothesized causal models must be interpretable and meaningful.

In conclusion, N-of-1 trials and research have often been described as "ahead of its time" [16], but few know about its methods or promise. Given the new guides for N-of-1 research, interest in personalized medicine/patient centered research, rise of personal health tracking, and novel self-directed N-of-1 studies, we believe the time has come for N-of-1 research to find its rightful place as a valuable complement to group research methodologies. We hope this special issue contributes to the spread of personal science and the propagation of N-of-1 research methods in medicine, informatics, and other areas of human investigation.

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