Measuring the meaningful

McNamara, John F; Davis, Joshua

Measuring the meaningful.

John F McNamara[1,2]

1. Department of Infectious Diseases, The Prince Charles Hospital, Chermside, Queensland, Australia

2. University of Queensland Centre for Clinical Research, Herston, Queensland, Australia

Joshua S Davis[3,4]

3. Menzies School of Health Research, Charles Darwin University, Casuarina, Northern Territory, Australia.

4. Department of Infectious Diseases, John Hunter Hospital, Newcastle, New South Wales, Australia.

Corresponding author: Joshua S Davis

Email: joshua.davis@menzies.edu.au

'People have the right and duty to participate individually and collectively

in the planning and implementation of their health care' (1). This declaration from the WHO

International Conference on Primary Health Care in 1978 resulted in the generation of health policy

statements in North America, Australia, Western Europe and the United Kingdom advocating

consumer involvement in healthcare (2). Patients have valuable first-hand knowledge of what it is

like to suffer an illness, though even today there is often limited patient input in clinical trial design,

potentially impacting on how translatable clinical research is.

The United States Federal Drug Administration recommends that assessment of how a patient feels

and functions should incorporate a directly patient-reported measure of perceived success (3).

Attempts to integrate patient experience into clinical trials has not translated well to infectious

diseases research. Despite an apparent persistent impact on patient function following bloodstream

infection (4) limited data exist regarding patient perception of successful treatment, functional

outcome and how they relate to currently used trial endpoints (5).

Mortality is the established gold standard in many infectious disease studies. It can be measured

objectively and is undeniably meaningful to patients. However, declining mortality rates or the study

of infections with very low mortality has meant demonstrating superiority or non-inferiority using

mortality endpoints may not be feasible. Thus, infectious diseases clinical triallists have generally

relied on surrogate outcome measures.

Duration of bacteremia has served as a surrogate outcome measure for *Staphylococcus aureus* bloodstream infection research for decades. The validity of this as a surrogate has been challenged. The CAMERA-2 trial of combination antibiotic therapy for MRSA bacteremia recently demonstrated that although duration of bacteremia was significantly decreased by the intervention, there was no mortality benefit (6).

How a patient feels, functions and survives should be the true endpoint against which to benchmark surrogate outcome measures, and provides an excellent conceptual starting point from which to frame a patient-centred outcome (7,8). In order to develop such outcomes, we need to ask patients directly about their experience and find ways to incorporate this into trials and clinical care.

In this context the study by King et al., published in this issue of Clinical Infectious Diseases, interviewed individuals who had suffered a bloodstream infection with *Staphylococcus aureus* or a gram negative bacillus (9). They used semi-structured interviews to explore patient experiences and potential differences between *Staphylococcus aureus* and a gram negative bloodstream infection. The study was designed to identify common patient experiences which may serve as substrates to develop patient-centred outcome measures for clinical trials.

The instruments used in this study are likely more familiar to the sociologist or psychologist than an infectious diseases clinician. Semi-structured interviews over 60 minutes captured a wide array of patient responses reflective of the diversity of individual experience. The researchers continued with data collection and analysis until the same ideas came up repeatedly and no new themes were emerging; this is referred to as thematic saturation. Achieving thematic saturation is important in

qualitative research, as failure to reach saturation has an impact on the interpretation of the research conducted (10).

Sixty-one interviews were completed, 31 *Staphylococcus aureus* and 30 gram negative bloodstream infections, achieving a 60% response rate which met the *a priori* target sample size. The majority of *Staphylococcus aureus* infections (73.4%) had a hospital length of stay of 14 days or less, and patients received a mean of 46.1 days of antibiotic therapy. Survival without recurrence was reported in 90% of patients during 90 days of follow up. Gram negative infections by comparison had a shorter length of stay and a shorter mean duration of antibiotic therapy of 21.3 days. Survival without recurrence in gram negative infections was over 90%.

Despite seemingly excellent outcomes from an objective and quantitative point of view, patients reported a prolonged and substantial negative effect on their quality of life. Survivors of *Staphylococcus aureus* in particular reported major impacts on quality of life domains. These included prolonged fatigue, emotional instability and loss of functional capacity. Post-traumatic stress disorder symptoms are a known sequela of sepsis (11) and the emergence of themes of anxiety, depression and suicidal ideation following bloodstream infection in King et al's study is as significant for clinical trials as it is for bedside clinical care.

Timing of interviews in relation to the episode of blood stream infection has a potential influence on findings of such research given issues with recall bias and memory impairment, particularly in older individuals. Furthermore, a change in the individuals' internal standards may occur over time, altering their perception of the episode. This change in internal standard is referred to as a response shift. An acute deterioration in function may be the catalyst for response shift in the individual (12).

As an example: deterioration in function (catalyst) leads to a realisation of a potentially life threatening illness. This in turn results in a response shift, as survival is no longer seen as guaranteed. Recalibration occurs, defining success not as how convenient or pleasant the treatment was but whether or not they have survived. This is perhaps apparent in King's study with knowledge of, or prior experience of a bloodstream infection limiting the level of impact on quality of life through expectation management. This has important implications for measuring patient-reported outcomes (13).

The inclusion of excerpts of patient narratives is fascinating and we would direct readers to take the time to review them. These shared experiences have value in normalising the experiences of patients we see with disseminated infection in our everyday clinical practice.

Those of us with a quantitative research background might initially dismiss a study enrolling "only" 61 patients; however, in qualitative research the numbers do not tell the full story. A qualitative study of this size is a substantial undertaking and, as King's study demonstrates, can shed valuable light on the subject of interest. It is important for those of us involved in designing and running clinical research studies to become familiar with qualitative research methods, and to aim to work *with* health consumers, not *on* health consumers, wherever possible (14).

In summary, traditional endpoints do not capture the entire picture for patients with blood stream infection. Whilst traditional measures remain essential, incorporating quality of life measurements and a patient voice in an integrated outcome metric is needed if we want to truly understand the effect of any given intervention on people with blood stream infection.

References

1. World Health Organization. Declaration of Alma-Ata International. In: International Conference on Primary Health Care, Alma-Ata, USSR, 6-12 September 1978. 1978.

2. Payne JM, D'Antoine HA, France KE, McKenzie AE, Henley N, Bartu AE, et al. Collaborating with consumer and community representatives in health and medical research in Australia: results from an evaluation. Heal Res Policy Syst [Internet]. 2011 Dec 14 [cited 2020 Mar 14];9(1):18. Available from: https://health-policy-systems.biomedcentral.com/articles/10.1186/1478-4505-9-18

3. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes [Internet]. 2006 Oct 11 [cited 2018 Nov 9];4(1):79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17034633

4. McNamara JF, Harris PN, Chatfield MD, Lorenc P PD. Measuring patient centred long term outcome following a bloodstream infection: a pilot study. Clin Microbiol Infect. 2019;

5. Harris PN, McNamara JF, Lye DC, Davis JS, Bernard L, Cheng AC, et al. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. Clin Microbiol Infect [Internet]. 2016 Nov 1 [cited 2017 May 21]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/27810466

6. Tong SYC, Lye DC, Yahav D, Sud A, Robinson JO, Nelson J, et al. Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia. JAMA [Internet]. 2020 Feb

11 [cited 2020 Mar 31];323(6):527. Available from:

https://jamanetwork.com/journals/jama/fullarticle/2760737

7.   Prentice RL. Surrogate endpoints in clinical trials: Definition and operational criteria. Stat Med

[Internet]. 1989 Apr 1 [cited 2020 Mar 14];8(4):431–40. Available from:

http://doi.wiley.com/10.1002/sim.4780080407

8.   Fleming TR, Powers JH. Biomarkers and Surrogate Endpoints In Clinical Trials. Stat Med

[Internet]. 2012 [cited 2020 Mar 14];31(25):2973. Available from:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3551627/

9.   King H, Doernberg S, Miller J, Grover K, Oakes M, Ruffin F, et al. Patients' Experiences with

Staphylococcus aureus and Gram-Negative Bacterial Bloodstream Infections: A Qualitative

Descriptive Study and Concept Elicitation Phase to Inform Measurement of a Patient-

Reported Quality of Life Outcome Measure. Clin Infect Dis. 2020;

10.   Morse JM. "Data were saturated . . . ";. Qual Health Res [Internet]. 2015 May 31 [cited 2020

Mar 14];25(5):587–8. Available from:

http://journals.sagepub.com/doi/10.1177/1049732315576699

11.   Wintermann G-B, Brunkhorst FM, Petrowski K, Strauss B, Oehmichen F, Pohl M, et al. Stress

Disorders Following Prolonged Critical Illness in Survivors of Severe Sepsis. Crit Care Med

[Internet]. 2015 Jun [cited 2020 Mar 14];43(6):1213–22. Available from:

http://journals.lww.com/00003246-201506000-00010

12.   Ahmed S, Sawatzky R, Levesque J-F, Ehrmann-Feldman D, Schwartz CE. Minimal evidence of

response shift in the absence of a catalyst. Qual Life Res [Internet]. 2014 Nov 5 [cited 2018

Nov 9];23(9):2421–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24899546

13.   Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life

research: a theoretical model. Soc Sci Med [Internet]. 1999 Jun [cited 2020 Mar

15];48(11):1507–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10400253

14.   Australian Clinical Trials Alliance. Toolkit for Researchers and Research Organisations

[Internet]. [cited 2020 Mar 31]. Available from:

https://involvementtoolkit.clinicaltrialsalliance.org.au/toolkit