

## **Clinical outcomes in intermittent claudication – time for a change?**

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# Clinical outcomes in intermittent claudication - time for a change?

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1 Efforts to treat intermittent claudication have inspired many interventions spanning surgery,  
2 pharmacology, medical devices and exercise therapy. These interventions are intended to  
3  
4 relieve symptoms, particularly pain induced by walking. This has motivated the prioritisation  
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6 of measures of walking performance as a primary outcome when examining treatment  
7  
8 efficacy. However, considering the sequelae of intermittent claudication, the impact of  
9  
10 impaired walking ability lies not in how far one can walk in discomfort but in how far one  
11  
12 cannot walk comfortably. Its impacts are defined by what it deprives from a person's life  
13  
14 rather than how far they can walk. The magnitude of this complex, individualised  
15  
16 phenomenon is best quantified by measuring disease-specific quality of life (QoL).  
17  
18 Fundamentally, QoL should be the primary endpoint in trials examining the efficacy of  
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20 treatments for intermittent claudication.  
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29 Why is this not the case?  
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31 Historically, walking assessments are used in clinical practice both as a diagnostic tool and  
32  
33 outcome measure. Walking assessments respond to interventions which address the  
34  
35 presenting complaint and underlying pathophysiology whilst providing an objective measure  
36  
37 of disease burden. The use of walking assessments for intermittent claudication trials predates  
38  
39 the development of QoL instruments. Only recently have patient-reported outcomes been  
40  
41 considered for achieving regulatory approvals for medical devices or pharmaceuticals.  
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46 Despite the development of several QoL tools since, there has been disparate application of  
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48 QoL instruments [1], leading to yet unmet calls for standardisation [2] and potential research  
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50 waste.  
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55 Another barrier to choosing QoL as a primary outcome measure is resource. QoL measures  
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57 can be less responsive than walking-based measures to conservative treatments [3] therefore  
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1 requiring larger sample sizes to detect a difference. Almost all trials powered using walking  
2 performance measurements have not been powered to detect changes in QoL. Exceptions  
3  
4 include the SUPER trial [4] (which did not recruit to target) and the CETAC trial [5]  
5  
6 (possibly the only adequately powered trial using QoL as a primary outcome in this field).  
7  
8 Until trials are delivered which are powered to assess changes in QoL outcomes, we rely  
9  
10 upon meta-analyses to determine the efficacy of interventions. This approach may conclude  
11  
12 that the only effective intervention is a combination of angioplasty and supervised exercise.  
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19 Finally, some might assume that changes in walking performance are adequate surrogates for  
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21 changes in QoL. Accepting this requires evidence to justify trial-level surrogacy; such  
22  
23 evidence does not exist. Limited evidence supports only a weak correlation between changes  
24  
25 in walking performance and changes in disease-specific quality of life [6]; most data  
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27 concerning this relationship remains unpublished.  
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34 Accepting these conclusions implies there is uncertainty regarding the magnitude of efficacy  
35  
36 and cost-effectiveness of many established interventions. There is a substantial remit to  
37  
38 improve research practices in this field. Standardising of the use of QoL instruments will  
39  
40 require international consensus – a laborious yet worthwhile endeavour. QoL as an outcome  
41  
42 measure is no panacea. Decisions about treatment consider the magnitude and durability of  
43  
44 potential gains in QoL alongside the costs of treatments and their mortality and morbidity  
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46 related risks. As yet, there is no core outcome set for intermittent claudication to direct  
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48 researchers to capture important outcomes in a standardised manner.  
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53 To evaluate whether changes in walking performance measures can act as trial-level  
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55 surrogates for changes in QoL we should encourage analyses of existing unpublished data  
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57 from major trials. Were sufficient evidence to emerge, the use of walking performance  
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measures as a primary outcome is justified. Should this relationship not hold; future trials may seek to re-evaluate existing interventions which may improve QoL irrespective of effects upon walking performance. Efforts to treat intermittent claudication are primarily efforts to improve QoL and our research choices should reflect this.

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