
■ REPLY

The use of surrogates as key performance indicators

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Sir,

Commenting on my article titled **Surrogates in chronic disease: misleading substitutes**, Dr Helena Sá shows herself greatly concerned with what she calls “*the radical view of the proposal by Dr José Vinhas, that denies the utility of adopting therapeutic thresholds as a tool to promote and evaluate optimal therapy adequacy in dialysis.*”

The letter raises two different kinds of issues:

1. Does measurement (through the use of Key Performance Indicators [KPI]) of Quality in Health Care worthwhile? Did I advocate for its futility?
2. If KPIs are useful, how can they be chosen? What requirements should they met?

To begin with, I must say that the article was not on KPIs but on the use of surrogates for clinical outcomes in the chronic diseases setting. Although I made some comments on the (inappropriate) use of surrogates in Quality Measurement Programmes, the article does not make any reference to the utility of, or absence of utility of, KPIs. The point of view advocated in the article was that surrogate markers should only be used after they have been validated by clinical trials. And that this holds true whether they are to be used in clinical trials, Clinical Practice Guidelines, or as KPIs in Quality Measurement Programmes.

Like Dr Helena Sá, I believe that KPIs are of utmost importance in Quality Measurement Programmes. But the use of surrogates as KPIs requires that they have previously been validated. Why is this? Because otherwise the use of surrogates to drive interventions may lead to useless or even harmful interventions. In the article I gave two examples:

In observational studies, higher haemoglobin levels and higher doses of dialysis have been associated with better outcomes. However, interventional studies that have raised haemoglobin levels with epoetin have shown an increased risk of cardiovascular events and no-effect on mortality¹⁻³, while interventional studies that have raised dialysis dose have also not been shown to reduce mortality⁴. Does this mean that I’m denying “*the utility of adopting therapeutic thresholds as a tool to promote and evaluate optimal therapy and adequacy of dialysis*”? By no means! Does this mean that they should not be used as KPIs?

Maybe not. Maybe this does not stand entirely true. Let us see:

■ Process of care: haemoglobin as a KPI

1. In the TREAT study², patients with type 2 diabetes and chronic kidney disease assigned to the placebo (receiving darbepoetin alfa as a rescue agent if the haemoglobin level fell below 9.0 g/dL) achieved a haemoglobin level of 10.6 g/dL (interquartile range, 9.9 to 11.3), while patients treated with darbepoetin targeting a haemoglobin of 13.0 g/dL achieved a haemoglobin level of 12.5 g/dL (interquartile range, 12.0 to 12.8). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group. Therefore, to target a haemoglobin level above 11.0 g/dL was not associated with an improvement in health-related quality of life;
2. Five relevant clinical trials have evaluated the effect of different haemoglobin targets on patient mortality^{1,2,5-7}. Lower haemoglobin targets in these studies were 10.6 g/dL (9.9 to 11.3) [achieved], 10.0 g/dL, 9.5 to 11.5 g/dL, 11.3 g/dL, 10.5 to 11.5 g/dL, respectively (Table I). Higher haemoglobin targets were not associated with decreased mortality. Therefore, to target a haemoglobin level above 9.5 to 11.5 is not associated with lower all-cause mortality;
3. Four relevant clinical trials have evaluated the effect of different haemoglobin targets on stroke^{1,2,5,7}. Lower haemoglobin levels in these studies were 10.6 g/dL (9.9 to 11.3), 10.0 g/dL, 11.3 g/dL, 10.5 to 11.5 g/dL, respectively (Table I). Higher haemoglobin targets were associated with increased risk of stroke. Therefore, to target a haemoglobin level above 9.9 to 11.5 may be associated with increased risk of stroke;
4. Two relevant clinical trials have evaluated the effect of different haemoglobin targets on vascular access thrombosis^{5,6}. Lower haemoglobin targets were 10.0 g/dL and 9.5 to 11.5 g/dL, respectively (Table I). Higher haemoglobin targets were associated with increased risk of vascular access thrombosis. Therefore, to target a haemoglobin level above 9.5 to 11.5 g/dL is associated with increased risk of vascular access thrombosis;
5. To target a haemoglobin level above 11.0 g/dL is associated with higher costs as compared with targeting a haemoglobin below 11.0 g/dL;
6. Additionally, the key criterion for the validity of a surrogate marker is the possibility to predict the effect of the treatment on the clinical outcome by the effect of the treatment on the surrogate. The data presented in the previous paragraphs shows that using haemoglobin as a target within the above specified ranges is not able to predict any significantly beneficial effect of the treatment, but may

Table I

Target Haemoglobin values (g/dL) in CKD trials with ESAs

	Lower target	Higher target
§NHT ^{***} (Ref 5)	10.0	14.0
§Parfrey <i>et al</i> ^{**} (Ref 6)	9.5 to 11.5	13.5 to 14.5
§CREATE [*] (Ref 7)	10.5 to 11.5	13.0 to 15.0
§CHOIR [*] (Ref 1)	11.3	13.5
§TREAT [*] (Ref 2)	10.6 (achieved)	13.0
Global	9.5 to 11.5	13.0 to 15.0

§ Trials evaluating the effect of ESAs on risk of all-cause mortality

*Trials evaluating the effect of ESAs on risk of stroke

**Trials evaluating the effect of ESAs on risk of vascular access thrombosis

predict some harmful effects of the therapy. Noteworthy, the harmful effects observed (stroke, VA thrombosis) were not the primary end points in those trials;

7. Based on the previous paragraphs, why would anyone want to target a haemoglobin value above 11.0 g/dL when the beneficial effect on health-related quality of life is irrelevant and the risk of deleterious effects seems to increase? Additionally, if the aim of anaemia treatment with ESAs is to reduce the need for red cell transfusion while avoiding harmful effects, why would anyone want to target a range of haemoglobin values?
8. Therefore, my proposal would be that for patients with CKD on dialysis, ESA treatment should be initiated in an individualised way (usually only when the haemoglobin level is below 10 g/dL), and if the haemoglobin level approaches or exceeds 11 g/dL, we should reduce or interrupt the dose of ESA. I would still use haemoglobin as a KPI, but the target value would be a threshold, not a range: the “proportion of patients (treated with ESAs) with a haemoglobin value ≥ 11.0 g/dL: 0%.”

■ Process of care: dialysis dose as a KPI

1. The dose of dialysis has been considered a surrogate marker based on the association between Kt/V or URR and all-cause mortality observed in epidemiological studies. However, interventional evidence showed that a higher dose of dialysis (target value: eKt/V of 1.45; achieved value: eKt/V of 1.53) has not been shown to reduce mortality, as compared with a lower dose (target value: eKt/V of 1.05; achieved value: eKt/V of 1.16)⁴. Whether an achieved equilibrated Kt/V below 1.2 is associated with increased mortality is a hypothesis that has never been tested in relevant clinical trials, and therefore, is unknown;
2. Interventional evidence has shown that morbidity was a discontinuous function of Kt/V, and that the risk increased below a single-pool Kt/V of 0.9⁸. This trial “validates” dialysis dose (as measured by Kt/V) as a surrogate marker for morbidity. However, interpretation of this study’s results has been hampered by methodological problems, such as the small sample size, the low number of events and the absence of pre-defined primary end points in a study with an open label design;
3. Taken together, these data suggest that targeting dialysis dose below a certain threshold may have deleterious effects on patients, although it is unclear what that threshold might be;
4. Current practice patterns include targeting a dialysis dose of eKt/V ≥ 1.2 . Evidence shows that this seems to be a safe target and one usually easily achieved;
5. Dialysis units should probably target an equilibrated Kt/V ≥ 1.2 ;
6. Therefore, I would still use dialysis dose measured by “the proportion of patients with an eKt/V ≥ 1.2 ” as a KPI, with a target value of 90%. However, it must be recognised that this indicator does not meet the requirements of a KPI, and therefore, the beneficial effect of using such target remains uncertain.

The National Commission for Monitoring of Dialysis (*Comissão Nacional de Acompanhamento de Diálise – CNAD*) has accomplished a critical review of the current Quality Measurement Programme, and has proposed the following metrics with 5 KPIs:

1. KPI: Annual mortality; Target value: $\leq 20\%$
2. KPI: Point prevalence of tunnelled catheters; Target value: 18%

3. KPI: Point prevalence of AVF plus PTFE; Target value: 82%
4. KPI: Haemoglobin levels; Target value: ≥ 9.0 g/dL and ≤ 12.0 g/dL
5. KPI: Dialysis dose as measured by eKt/V or URR; Target value: ≥ 1.2 or $\geq 65\%$, respectively.

I have already commented on the KPIs included under Paragraphs 4 and 5. The critical question in Paragraph 4 is: what is the evidence supporting a threshold for target haemoglobin level of ≤ 12.0 g/dL? What is the evidence supporting a target range for haemoglobin? Apparently, the answer is “none” for the first, as well as for the second question.

What about Paragraphs 1 to 3?

■ Paragraph 1 – Clinical outcome: annual mortality as a KPI

1. Patient all-cause mortality in Portuguese dialysis units has been decreasing in recent years. Currently, annualised all-cause mortality in the country is 14%. Therefore, a target value $\leq 20\%$ is completely futile;
2. All-cause mortality has a wide range of variation, depending on demographic factors and comorbidities. The definition of a target value of all-cause mortality $\leq 20\%$, which is **equal for all units**, is inappropriate: it is too high for private units (national mortality in 2011: 11.8%), and probably too low for public units (national mortality in 2011: 29.4%). Unadjusted mortality is meaningless;
3. Unfortunately, in dialysis patients, no intervention has shown to improve patient outcomes. Therefore, in my opinion, mortality should not be used as a KPI.

■ Paragraphs 2 and 3 – Process of care: haemodialysis vascular access as a KPI

1. Most people would agree that we should strive for a progressively increased prevalence of arterio-venous fistulas (AVF). KPIs should be used as a tool to attain this goal. Pooling together AVF and PTFE as a KPI (as CNAD does), does not drive interventions in that direction. Data from the Registry of the Portuguese Society of Nephrology show that a target of 75% prevalence of AVF may be achieved in the Portuguese population (data from northern areas of Portugal);
2. Data from the Registry of the Portuguese Society of Nephrology show that a target of 15% prevalence of tunnelled catheters may be achieved in the Portuguese population (data from southern areas of Portugal);
3. Portuguese dialysis units should target a $\geq 75\%$ point prevalence of AVF and a $\leq 15\%$ point prevalence of tunnelled catheters.

■ Patient safety: nosocomial infection as a KPI

In the domain of patient safety, I would propose the following additional KPIs:

1. Hepatitis B (KPI: hepatitis B virus infection; Target value: Yearly incidence of hepatitis B virus infection: 0%)
2. Hepatitis C (KPI: hepatitis C virus infection; Target value: Yearly incidence of hepatitis C virus infection: 0%)

Table II

Proposed Quality Measurement Programme for End-Stage Renal Disease

Domain	KPI	Individual target value	Facility target value
Process of care	Haemoglobin	<11.0 g/dL	100%
	AVF (annualised; point prevalence)	NA	≥75%
	Tunnelled catheters (annualised; point prevalence)	NA	≤15%
	Dialysis dose (eKt/V or URR)	≥1.2 or ≥65%	90%
Patient safety	Hepatitis B (annualised; health care-acquired)	0	0%
	Hepatitis C (annualised; health care-acquired)	0	0%
	Bacteraemia (annualised; health care-acquired)	0	<0.7 per 100 patient-months
Patient-reported outcomes	SF36?	?	?

3. Bacteraemia (KPI: Bacteraemia secondary to nosocomial transmission; Target value: Incidence of bacteraemia secondary to nosocomial transmission: <0.7 per 100 patient-months)

I would like to finalise by showing in Table II the proposed metrics of the ESRD Quality Measurement Programme. Although the inclusion of a patient-reported outcome as a KPI was not discussed in this letter due to space concerns, it is a critical domain within a Quality Measurement Programme.

How a Quality Measurement Programme can be turned into a Quality Incentive Programme is a distinct issue that is beyond the scope of this letter, but will certainly be the core of ensuing debate.

Conflict of interest statement.

Dr Jose Vinhas has received consultancy fees from Abbott, Amgen, F. Hoffmann-La Roche, Janssen-Cilag and NephroCare. He has received speaker's honoraria from Amgen, F. Hoffmann-La Roche and Renal Pharma.

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