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**Supplementary materials for:**

**“The reporting of treatment non-adherence and its associated impact on economic evaluations conducted alongside randomised trials: a systematic review”**

Samuel L Brilleman

Chris Metcalfe

Tim J Peters

William Hollingworth

This document includes:

- Table S1. Intervention (and study population) for trials with one-off interventions included in the “Other” category
- Table S2. Intervention (and study population) for trials with recurring interventions included in the “Other” category
- Appendix: Calculation of the incremental cost-effectiveness ratio (ICER) and net monetary benefit statistic (NMB) in the presence of non-adherence
- Full list of articles included in the systematic review

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**Table S1.** Intervention (and study population) for trials with one-off interventions included in the “Other” category

Study Population	Intervention (experimental treatment arm)
Patients with acute anterior shoulder dislocation	Intra-articular lidocaine
Cirrhotic patients	Percutaneous ethanol injection (PEI)
Patients aged 50 to 70 undergoing a routine physical exam with their primary care provider	Tailored interactive computer-based intervention intended to improve colorectal cancer screening
Joints with inflammatory arthritis	Sonographic image-guided injection
Adult patients with a simple laceration wound	Wound closure by tissue adhesive (Dermabond)

**Table S2.** Intervention (and study population) for trials with recurring interventions included in the “Other” category

Study Population	Intervention (experimental treatment arm)
Patients with subacute nonspecific neck pain	Behavioral graded activity with a physical therapist (increasing level of activity each time)
Patients with hard to heal leg ulcers	Ultrasound treatment plus usual care
Patients with verrucae (plantar warts)	Cryotherapy using liquid nitrogen
Mechanically ventilated intensive care patients	Open endotracheal suctioning (inpatient setting)
Elderly patients with skin tears	Tegaderm Absorbent
Patients with progressive CKD	Early start of dialysis therapy
Patients with severe mental illness receiving outpatient or community psychiatric care	Individual placement and support programme
Adults presenting with back pain	StartBack screening tool which is used to provide stratified management of back pain based on prognosis (low, medium or high risk)
Patients with stage 3 to 4 CKD	Chronic disease management model for CKD (a nephrologist/nurse–based multifaceted intervention for stage 3 to 4 CKD)
People at higher risk of developing diabetes	Diabetes prevention program - lifestyle intervention (included group education sessions, physiotherapy, peer support sessions, telephone contact)
Patients who have undergone primary total knee athroplasty	Multidisciplinary rehabilitation group
Patients (aged over 45 years) with COPD	Pharmacy-led education and self-managment programme
Women who have recently completed breast cancer treatment	Nurse-led telephone follow up (3, 6, 9 months) plus 12 month mammography and outpatient visit [Factor

	1] AND a short educational group programme (EGP, 2 x 2.5 hour sessions) [Factor 2]
Patients with hypertension (not under control)	Telemonitoring of home blood pressure
Patients untreated for osteoporosis 1 year after wrist fracture	Nurse case-manager
Patients who underwent open heart surgery	Procalcitonin-guided antibiotic treatment (PCT-group)
Patients presenting at the emergency department with intermediate risk acute chest pain	Stress cardiac magnetic resonance (CMR) observation unit testing
Patients who have undergone discectomy or lateral nerve root decompression surgery	Rehabilitation programme & educational booklet
Malnourished patients with benign gastrointestinal disease	Oral nutritional supplements + dietary counselling on hospital discharge (baseline)
Patients with hyperthyroidism	High dose regimen of I-131 treatment (a form of radiotherapy)
Children (16 years or less) with diagnosed eczema	Care by a nurse practitioner
Patients curatively operated for colorectal cancer	Follow up by a specialist nurse
Children with atopic eczema	Water softener installation plus usual care
Patients undergoing segmental colectomy	Laparoscopic colectomy & fast track care
Patients with osteoarthritis to the knee	Acupuncture plus advice leaflet and 6 exercise sessions (acupuncture included with exercise sessions)

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**Appendix:** Calculation of the incremental cost-effectiveness ratio (ICER) and net monetary benefit statistic (NMB) in the presence of non-adherence

Scenario: We assume that in an RCT of surgery versus medical care a proportion  $(1-p)$  of patients would not adhere surgery, were they to be randomised to it and due to randomisation the proportion will be equal in each arm of the trial. Those who will adhere to surgery (adherers) have higher costs ( $C_{S,A}=\text{£}5,000$  versus  $C_{M,A}=\text{£}2,000$ ) and better outcomes ( $E_{S,A}=2$  QALYs versus  $E_{M,A}=1.6$  QALYs) if randomised to surgery rather than medical care (see Table A3). Those who will not adhere with surgery if randomised to it (non-adherers) will have identical costs ( $C_{S,NA}=C_{M,NA}=\text{£}2,000$ ) and outcomes ( $E_{S,NA}=E_{M,NA}=1$  QALY) whether they are randomised to surgery or medical care. All patients will comply with medical care if randomised to it, but outcomes of medical care are assumed to be better in those who would have adhered to surgery than in those who would not (1.6 QALYs versus 1 QALY).

Table S3. Costs and outcomes of therapy under the assumed scenario

	Surgery		Medical care	
	Adherers	Non-adherers	Adherers	Non-adherers
Cost	£5,000	£2,000	£2,000	£2,000
QALY	2	1	1.6	1

The incremental cost-effectiveness ratio (ICER) and the net monetary benefit statistic (NMB) can then be calculated under this scenario using either an intention to treat (ITT) or per protocol (PP) analysis set. If  $p = 0.5$  and willingness to pay for a QALY ( $\lambda$ ) = £20,000 then:

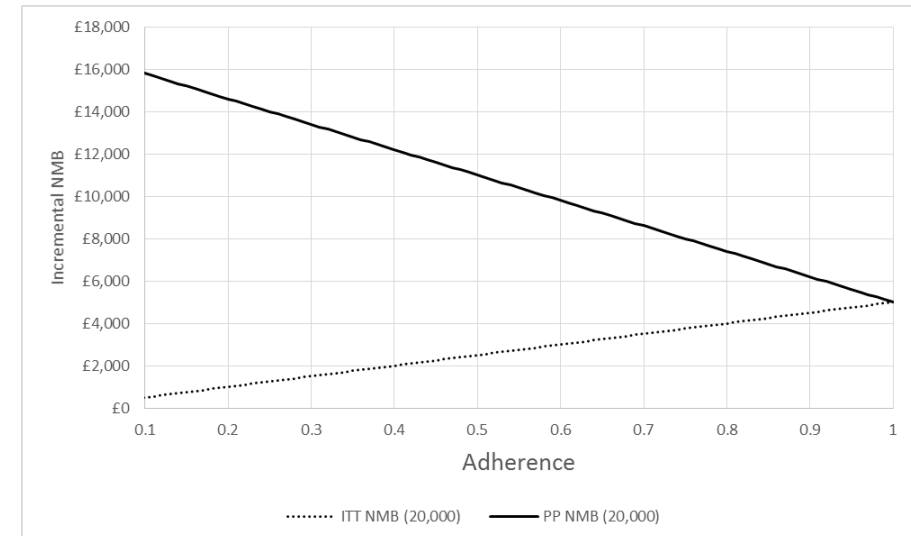
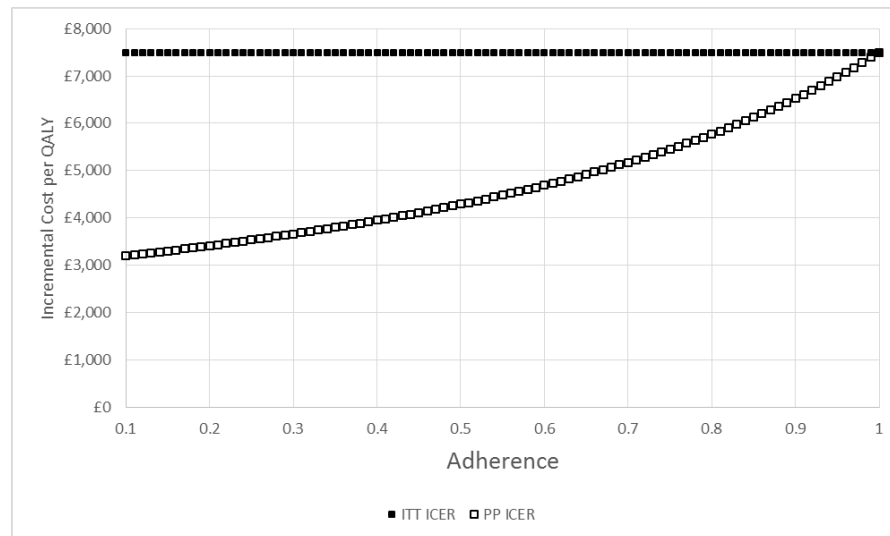
$$\text{ITT ICER} = \frac{(pC_{S,A} + (1-p)C_{S,NA}) - (pC_{M,A} + (1-p)C_{M,NA})}{(pE_{S,A} + (1-p)E_{S,NA}) - (pE_{M,A} + (1-p)E_{M,NA})} = \text{£}7,500$$

$$\text{PP ICER} = \frac{C_{S,A} - (pC_{M,A} + (1-p)C_{M,NA})}{E_{S,A} - (pE_{M,A} + (1-p)E_{M,NA})} = \text{£}4,286$$

$$\text{ITT NMB} = ((pE_{S,A} + (1-p)E_{S,NA}) - (pE_{M,A} + (1-p)E_{M,NA})) \cdot \lambda - ((pC_{S,A} + (1-p)C_{S,NA}) - (pC_{M,A} + (1-p)C_{M,NA})) = \text{£}2,500$$

$$\text{PP NMB} = (E_{S,A} - (pE_{M,A} + (1-p)E_{M,NA})) \cdot \lambda - (C_{S,A} - (pC_{M,A} + (1-p)C_{M,NA})) = \text{£}11,000$$

The left and right figures below, respectively, show the ICER and NMB across a range of adherence ( $p$ ) values:



Under this scenario we see that the ITT ICER is insensitive to large changes in adherence. In fact, under our previous assumptions that the proportion  $(1-p)$  of patients who would not adhere to surgery is the same in each arm of the trial (due to randomisation) and that costs ( $C_{S,NA} = C_{M,NA}$ ) and outcomes ( $E_{S,NA} = E_{M,NA}$ ) non-adherers are identical no matter which treatment they are randomised to, it can be shown that:

$$\begin{aligned}
 \text{ITT ICER} &= \frac{(pC_{S,A} + (1-p)C_{S,NA}) - (pC_{M,A} + (1-p)C_{M,NA})}{(pE_{S,A} + (1-p)E_{S,NA}) - (pE_{M,A} + (1-p)E_{M,NA})} \\
 &= \frac{(pC_{S,A} - pC_{M,A})}{(pE_{S,A} - pE_{M,A})} \\
 &= \frac{p(C_{S,A} - C_{M,A})}{p(E_{S,A} - E_{M,A})} \\
 &= \frac{C_{S,A} - C_{M,A}}{E_{S,A} - E_{M,A}} \\
 &= \text{ICER}_A
 \end{aligned}$$

$$\begin{aligned}
 \text{ITT NMB} &= \left( (pE_{S,A} + (1-p)E_{S,NA}) - (pE_{M,A} + (1-p)E_{M,NA}) \right) \cdot \lambda - \left( (pC_{S,A} + (1-p)C_{S,NA}) - (pC_{M,A} + (1-p)C_{M,NA}) \right) \\
 &= (pE_{S,A} - pE_{M,A}) \cdot \lambda - (pC_{S,A} - pC_{M,A}) \\
 &= p \left( (E_{S,A} - E_{M,A}) \cdot \lambda - (C_{S,A} - C_{M,A}) \right) \\
 &= p \text{ NMB}_A
 \end{aligned}$$



where  $ICER_A$  and  $NMB_A$  are, under the assumptions discussed, unbiased estimates of the incremental cost-effectiveness ratio and the net monetary benefit in adherers. In other words the ITT ICER is an unbiased estimate of the cost per QALY in patients who adhere to treatment, regardless of the adherence rate in the trial. On the other hand, the ITT NMB changes proportionately with the adherence rate. The implications of this are that the ITT ICER is not a particularly good measure for informing policy, particularly in trials with large non-adherence. The NMB statistic however does take account of non-adherence and therefore is the approach we would recommend for ITT cost-effectiveness analyses aimed at informing policy. Since under PP analysis patients who won't adhere to surgery are excluded from the surgery arm but not the medical care arm, the PP estimates are biased and generally should be avoided, particularly in the context of trials aimed at informing policy.

We recognise that if the policy is to accept an ICER less than a given willingness to pay threshold (for example  $\lambda = \text{£}20,000$  per QALY) or to accept an NMB greater than zero, then for an RCT with a single new intervention both the ITT ICER and ITT NMB will in fact lead to the same policy decision. This is the case since the  $ITT\ ICER < \lambda$  if, and only if, the  $ITT\ NMB(\lambda) > 0$  for all possible adherence rates (see proof at the end of this appendix). However, if a policy maker is trying to decide which of two or more new interventions (for example drug A or drug B) is more cost-effective on the basis of the results of two RCTs (drug A versus placebo; drug B versus placebo), then the two ITT ICERs will potentially be misleading in the presence of varying adherence to therapies.

It is also worth emphasising that only some of the assumptions in our scenario are necessary conditions for the algebraic results to hold. This includes our assumption that the proportion  $(1-p)$  of patients would not adhere surgery is the same in each treatment arm (due to randomisation) as well as our assumption that non-adherers will have identical costs ( $C_{S,NA} = C_{M,NA}$ ) and outcomes ( $E_{S,NA} = E_{M,NA}$ ) regardless of which treatment arm they are randomised to. However other assumptions in our scenario are required only for numerical calculations and are not in fact necessary for deriving the algebraic results

regarding the ITT ICER and ITT NMB. This includes our assumption that all patients will adhere to medical care if randomised to it as well as our assumption that outcomes of medical care are better in adherers than non-adherers (1.6 QALYs versus 1 QALY).

NB. Proof showing the ITT ICER  $< \lambda$  if and only if the ITT NMB( $\lambda$ )  $> 0$  for all possible adherence rates:

$$\text{ICER}_A < \lambda$$

$$\Rightarrow \frac{C_{S,A} - C_{M,A}}{E_{S,A} - E_{M,A}} < \lambda$$

$$\Rightarrow (E_{S,A} - E_{M,A}) \cdot \lambda - (C_{S,A} - C_{M,A}) > 0$$

$$\Rightarrow \text{NMB}_A > 0$$

$$\Rightarrow p \text{NMB}_A > 0 \quad \forall p > 0$$

### **Full list of articles included in the systematic review**

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