Crippled by Inertia? Uncertainty and Optimal Decision Making in the Treatment of Non-Healing Wounds

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Introduction

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- Wound Care represents a major health economic issue to the NHS
  - Chronic wounds big drivers of costs
- There are 1,000s of products since 2000
  - But evidence base is not trusted
  - Nothing gets adopted because evidence is too uncertain.
- Is this an optimal decision strategy?
  - Economists have developed new way of formally incorporating uncertainty in decision making framework
  - Applied to an evaluation haemoglobin spray
  - **Are we (the NHS) too conservative in our approach to decision making? Does this limit productivity?**

Chronic Wounds

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- Chronic non-healing wounds are estimated to cost $20bn per annum in the United States and £5bn to the NHS in the UK.
- In Europe the average cost per episode is estimated at €6,650 for leg ulcers and €10,000 for foot ulcers which accounts for 2–5.5% of health-care budgets.
- 88% of patients with chronic wounds receive care from nurses and it is estimated that wound management takes over 50% of community nurse time. This represents a non-marginal use of a scarce resource at a time following a 39% reduction in district nurses in the UK over the period 2002-2012
- 39% of wounds in the UK remain unhealed after one year

An Uncertain/Misleading Evidence Base

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- Despite 1,000s of products, trials and observational studies evidence base still considered very poor even misleading:
  - Inadequate sample sizes, short follow-up periods, non-random allocation to treatment groups, non-blinded assessment of outcomes, and poorly described control groups and concurrent interventions
  - Cullum et al (2016) find that 41% of trials specified no primary outcome, an astonishing 94% of trials finding significant differences were subject to some sort of bias - conclude research agenda is therefore infinite
- Madden (2012) paints a picture of an evidence base that has been unduly influenced by ‘corporate science’
  - the production of misleading evidence and investigation designed to look like peer-reviewed academic work.
- Current practice is to choose cheapest dressing unless compelling evidence dictates otherwise

Uncertainty within a decision-making framework

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- Health economists have established an analytical cost-effectiveness framework for decision making
  - As enshrined in the NICE Reference Case Model
    - Incremental costs per QALY (ICER)
- They also used to argue uncertainty was important to value and quantify but was ***essentially a totally separate issue*** (Irrelevance of inference 1999)
  - Adopt apparently cost-effective technologies
  - Quantify uncertainty via (Probabilistic) Sensitivity Analysis and work out ***costs, consequences and value of uncertainty***
  - Decide whether to collect further information
- Though the methods of quantifying importance of uncertainty are all adopted few really 100% believed the ***separate issue*** statement though there was no means of adopting alternative approaches to uncertainty within ICER framework

A comprehensive solution

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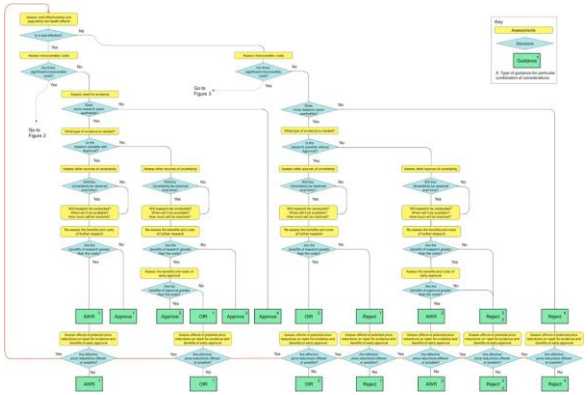
- 2016 saw publication of a comprehensive algorithm for including uncertainty within a decision analytic framework.

1. Based on current evidence is the technology expected to be cost-effective?
2. Are there significant irrecoverable costs?
3. Does more research seem worthwhile?
4. Is the research possible with or without approval?
5. Will other sources of uncertainty resolve over time?
6. Are the benefits of research greater than the costs of research?
7. Are the benefits of approval greater than the expected value of research?



- It outlines the conditions in which technologies should be adopted (or not or with evidence development) even with uncertainty – the key element is that it is a balance of costs, outcomes, likelihood of outcomes and ability to change ones mind if further evidence becomes available

Claxton, K., et al., A Comprehensive Algorithm for Approval of Health Technologies With, Without, or Only in Research: The Key Principles for Informing Coverage Decisions. Value Health, 2016. 19(6): p. 885-891.

For example

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- If a technology looks cost-effective but creates large sunk costs then it would be optimal to reject if sufficiently uncertain, even if further evidence can be created

- If a technology looks cost-effective and does not create large sunk costs then the optimal decision is either to adopt or adopt with evidence development
  - depends on the extent of uncertainty and ability to generate further evidence.
  - *In such cases the optimal decision is never to not adopt.*

The conventional way of thinking about uncertainty

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- That which can easily be captured by probabilistic statements
  - i.e. a toss of a ‘fair’ coin
  - Incorporated within HE via Probabilistic Sensitivity Analysis
  - Easily incorporated within Claxton algorithm

- Can we accommodate difficult to quantify ‘suspicion’ within the Claxton algorithm?

Classifying Other Uncertainty

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Pop Haydn : Medicine Pitchman and founder of school for scoundrels

- If the game is fair and you are convinced you know which shell is correct
- If the game is fair but you recognise additional uncertainty created by showman, but you have good eyes - a 50%+ chance of getting it right?
- If the game is fair but the showman is too quick for your eyes then a 33% chance of getting it right.
- The game is rigged - 0% chance of getting it right
- Depending on costs & prizes it may well be optimal to play in first three situations – you need to do the maths
  - Especially if the game is repeated and we can generate better evidence!

A Wound Care Example

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- A haemoglobin spray (Granulox) costing £125 per can with 30 applications
  - Conservative assumptions lead to increased cost per wound dressing of £6
- Evidence provided by 2 small scale RCTs in Mexico and Czech Republic and an observational study in the UK of 40 DFU patients across 2 years
  - 1 year first 20 patients treated with conventional treatment
  - 2nd year first 20 patients treated with conventional treatment + spray
  - No statistically significant differences between cohorts in mean patient characteristics such as wound size and duration
- Evidence suggests quicker healing rates with fewer dressing changes for unhealed wounds (2 per week vs 3 per week)
  - Results statistically significant

Conservative DFU Economic Model

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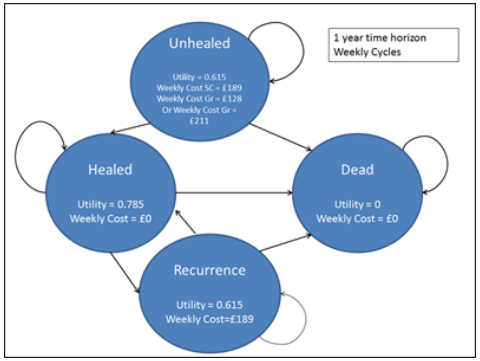

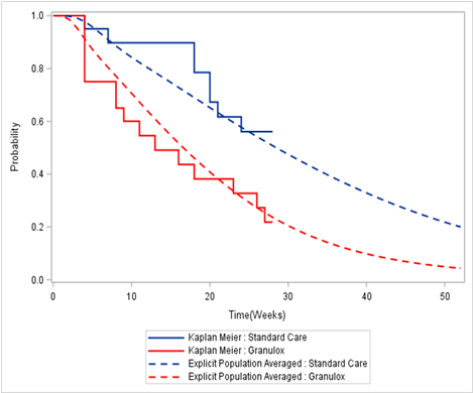

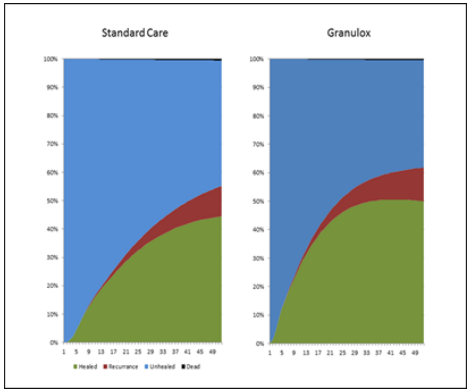

- Based on 40 patient observational study
  - Outcomes as if all treated with std care vs outcomes if all treated with Std Care + Spray
- 4 state markov model over 52 weeks
  - Amputations omitted
- Recurrence, death probabilities and state Utility values from external literature
- Unhealed → Healed populated by parametric survival model accounting for patient characteristics
  - Addresses possible imbalance in cohorts
- Dressing costs estimated at £57 for SC and £63 for SC + spray
  - Vast majority of cost = nurse time
- Green areas in Markov Trace represent healed wound patients

Results

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- Haemoglobin Spray is cost-effective it ‘dominates’
  - Creates better QoL and saves £2,868 on average over year
- Very robust to standard sensitivity analysis
  - Spray is cost-effective without improved healing rate or without reduced dressing or an 83% reduction in measured effectiveness of both
- But how does it stack up with difficult to quantify uncertainty?
  - **Although this is our analysis it is an industry sponsored submission!**

Cost of Uncertainty

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- 26,000 new chronic DFUs per annum
  - 2.6 million Type II diabetes patients in UK
  - 1 in 20 will develop foot ulcer in any given year
  - Of which 15% will develop into a chronic foot ulcer

- If spray is as effective as (conservatively) modelled
  - Cost savings of £2,868 per patient not realised …. **£74.5 million per annum** at a population level
  - Ignores cost savings from amputations avoided
  - QALY loss of 0.017 per patient or £14 million per annum if valued at £30k per QALY at population level

- If spray is not at all effective
  - Increased cost of £805 per patient; £21 million per annum at a population level

- Resolving uncertainty is therefore extremely valuable

Positions on Evidence and Optimal Decision Outcomes

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Scenario	Summary	Optimal Decision if Evidence Development is viable	Optimal Decision if Evidence Development is not viable
a) Accepting of data and model	Technology is likely to be cost-effective ; no irrecoverable costs; no uncertainty	Adopt	Adopt
b) Sceptical of data and model	Technology is likely to be cost-effective; no irrecoverable costs; high value of uncertainty	Coverage with Evidence Development	Adopt
c) Dismissive of data and model	Technology is not likely to be cost-effective; no irrecoverable costs; high value of uncertainty	Coverage with Evidence Development	Reject
d) Completely dismissive of data and model	Technology is not likely to be cost-effective; no irrecoverable costs; no or low value of uncertainty	Reject	Reject

- Is it reasonable to think d) or even c)?
  - Gottrup et al (2017) classify the evidence on Granulox as Grade 1B, the second highest score on the GRADE approach to treatment recommendation
  - Consensus recommendation from a working group of key UK opinion leaders found that the evidence was sufficient to recommend Granulox as a treatment (Chadwick et al 2015)

Conclusion – are we too conservative?

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- Evidence Based Medicine is not simply a rejection of everything that contains uncertainty.
  - It is a balanced evaluation of the probabilities, costs, opportunities foregone and the ability to change decisions with new evidence and without generating substantial sunk costs.
  - Developments in Health Economics allow greater insight and a better chance of making better decisions
  - Applying this methodological advance to the area of wound care technology would appear to be a step in the right direction. Though care should be taken in application
  - Where there is costly uncertainty the NHS may need to be more pro-active in resolving that uncertainty otherwise it risks perpetuating a situation of creating substantial unnecessary costs and loss of quality of life over time.
  - Simple conservative heuristics are unlikely to be optimal and maximise productivity

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