NICE judgment: good law risks bad science

(Bird, Matthews, Muniz in Lancet Neurology 2007; 6: 843-844)

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The Government has made the right decision.

Now it's your turn.

- AVONEX® delays progression to key disability milestones[1]
- 32% reduction in relapse rate[2]
- Significant reduction in the risk of cognitive deterioration[3]
- Low potential for NAb formation[4]

Once-a-week

AVONEX®

Interferon beta-1a, IM injection weekly

MAKE A DIFFERENCE

1st statistician to serve on NICE Appraisal Committee (1999-2005)

previously served on Medicines Commission (1991-1995);

previously served on RSS Working Party: Statistics and Statisticians in Drug Regulation in the UK (1990-1991).

1. **Hip replacements** ⇔ device licensing based on short-term failure rates; **RSS/NICE workshop** on survival modelling for artificial hips; time-horizon of 5, 10, 20 years ⇔ **NICE research-recommended UK Hip Registry . . .** {much missed: registry of breast implants}

2. **Multiple Sclerosis Drugs' ICERs from £10,000 to $1million** ⇔ "medical {statistical} disobedience" . . . 1-year study interposed . . . MS Society survey of patients' cognition on/off medication. {DH's disastrous cost-sharing}

3. **Alzheimer Drugs (1st Appraisal)** ⇔ **NICE recommended memory clinics + audit of "NICE eligibility criteria" . . .**

4. **Alzheimer Drugs (re-Appraisal)** ⇔ "medical {statistical} disobedience" . . . Individual patient meta-analysis across trials/class effect.

5. Locked Science

(science behind bars)

=

Bar on Science

Procedural unfairness: NICE challenged at Royal Courts of Justice before *Mrs Justice Dobbs*

NICE had provided "read only" version, *rather than fully executable version,* of the economic model *on which NICE Appraisal decision was based.*

1. Policy was to provide read-only version unless assessment team permitted otherwise;
2. No requirement for consultees to see every document;
3. Because 2 members of **Appraisal Committee** had access to fully executable version, Eisai was in similar position to other members of Appraisal Committee;
4. Model's assumptions were disclosed;
5. Information disclosed allowed for trenchant criticism, model was run with alternative assumptions, and output was compatible with Eisai's model with same or similar assumptions;
6. Eisai's submission to **NICE Appeal Panel** set out why not possible to understand model, yet also explained reasons why model was perverse, which suggested understanding of model;
7. No other body alleged unfairness re "read only";
8. No other consultee asked for fully executable version.

Reasoning by Mrs Justice Dobbs

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Counter-arguments: good law risks bad science

1) **NICE requires executable version of every health economic model by HTA teams or consultees. Why?**

1.1 make robust checks on implementation;

1.2 run sensitivity analyses;

1.3 make between-model comparisons;

1.4 enable additional outputs, as needed for the most astute scientific scrutiny.

If health economic model is wrong because

a) too simplistic ***or*** *b) marred by inadvertent errors,*

and there are many ways in which ***either*** *can happen,*

then Appraisal Decision might need to be reversed.

Counter-arguments: good law risks bad science

2) NICE did not disclose the executable version of "the" economic model to Eisai for reasons of intellectual property.

Who refused and why?

2.1 good science needs best criticism: wherever found;

2.2 peer review of HTA report, **detailed QA by NICE technical lead**, overview by ***Appraisal Committee*** and by ***non-industry consultees*** **might - all four - miss a technicality, either in epidemiology or health economics, that specialists in industry will spot;** ***(cf has happened . . . spotted by HTA itself)***

2.3 only one person has to find fault substantively in a scientific proposal, not a committee; ***(cf SMB out-voted . . .)***

2.4 not all parties would consider themselves able to use executable version, so that valid request should not require that most interested parties make it.

Not in the best interest of scientific rigour to argue

a) because no other body alleged unfairness ***and*** *b) no other party asked for fully executable version,*

then there was no requirement to fulfil "A" request for executable version.

Counter-arguments: good law risks bad science

3) No statutory obligation of disclosure. However:

3.1 all consultees should now be wary of any institution that, from outset, is unwilling to give permission to NICE to provide an executable version of the health economics model – *if NICE's Appraisal decision relies on this* – to industry partners or others in the consultation process;

3.2 HTA teams are paid for their consultancy work: the price of their service must include some sacrifice of academic freedom in the wider public interest ⇔ *as in SARS-CoV-2*.

3.3 full disclosure is necessary because HTA teams' work has important immediate effect: on patients, but also on revenues and research priorities of pharma.

3.4 full disclosure of HTA teams' influential work should be neither denied nor delayed to fit in with academic publication schedules.

NICE has nothing to hide. In future, ensure provision of executable version.

NICE has enviable reputation for transparency, eg rationale behind decisions. Thro' leadership and actions, time & again, NICE has shown its adherence to sound scientific principles.

SARS-CoV-2 ~ who advises ~ SAGE

RSS Working Party on in-vitro diagnostic tests.

Issues

self-certification by test-developer vs regulation by MHRA;
MHRA's Target Product Profiles;
level playing field for **independent evaluation** of rival tests;
transparency about evaluation-designs & test-performance **;
publicly-available in-context **results before** purchase/roll-out in UK.

** **laboratory** vs field-studies;
persons hospitalized with COVID-19 vs symptomatic vs asymptomatic screening;
age-group & **gender**;
venous vs capillary blood (antibody testing);
within-person trajectory for persistence of antibodies;
saliva vs nasopharyngeal swab (antigen testing);
for surveillance vs diagnosis;
for self-test & reading vs administered by HCW & read expertly.

SARS-CoV-2 antigen positives: Liverpool's mass screening of citizens (including @ schools) who are asymptomatic

Past RSS Working Parties

Statistical Issues in First-in-Man Studies (2007)
Open protocol as standard

Performance Monitoring in the Public Services (2003)
heed experimental design;
public protocol for performance evaluation
(NB: perverse consequences)

Official Statistics: Counting with Confidence (1991)

Liverpool?

Liverpool's mass screening for asymptomatic adult citizens:

INNOVA rapid test's late-evaluation in 43 asymptomatic positives

- **Liverpool protocol?** Eg Randomization to rapid test [Innova vs B] with one-third also randomized to cross-checking by RT-PCR [includes randomized swab-order: RT/rapid vs rapid/RT] **PLUS** all rapid-test positives confirmed by RT-PCR [requires second-swab, if not already randomized to one-third @ 2nd swab]

Number randomized: per 90,000	INNOVA	Rapid-test B	RT-PCR	RT-PCR swab for all rapid positives
30, 000	**		Randomized comparison: # positive (%)	*
30,000		**		*
7,500 (rapid/RT)	* 1		* 2	Prior expectation: 25 to 100 positives
7,500 (RT/rapid)	* 2		* 1	
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7,500 (RT/rapid)	* 2		* 1	

Mephedrone vs Cocaine/Ecstasy: switch began in 2008 or 2009 ?

British Army: Mercer's PQs (autumn 2009 & spring 2010) on Cocaine positive rate in Compulsory Drug Tests (CDTs)				
Year	Quarters	Number of CDTs	Cocaine Number C-positive CDTs	Cocaine C-Rate per 1000 (95% CI)
2008	Q1+2+3	**64** 650	**339**	**5.2** (**4.7** to 5.8)
	Q4	**25** 189	**88**	**3.5** (**2.8** to **4.2**)
2009	Q1+2+3	**78** 187	**190**	**2.4** (2.1 to **2.8**)
	Q4	**24** 762	**47**	**1.9** (1.4 to 2.4)

NHS-Digital alternative to legislation in E&W
⇔ ONS, NHS-Digital & RSS investigate . . .

NHS Digital holds informal dates of death on its personal Demographics Service (PDS-DOD).

National Statistician-approved-use if PDS-DOD vs ONS-DOD is both more timely & reasonably accurate. ***Investigation: ONS-DODs in 2011-15.***

Around 0.5 million deaths pa in E&W:

PDS-DOD was MISSING for 40% in 2011; MISSING for 28% in 2015.

Agreement (*when PDS-DOD available*) with ONS-DOD:

EXACT for only 694,786 (76%) of 918,214 deaths in 2011-13;
to within 7 days for 895,032 (97.5%).

Recommendations made: RSS Belfast. But RSS renews legislation-call.

SMB's MRC-BACKGROUND

Mar 2005: Fatal Accident Inquiry into prisoner death HMP Kilmarnock

Mar 2006: UK statistical indifference to military fatalities

Dec 2007: British Army's CDTs battalion lost to cocaine positives ⇔ TODAY ⇔ Patrick Mercer MP

June 2008: Long waiting times for military inquests ⇔ Patrick Mercer MP

2009: H1N1 & Cocaine CDTs ⇔ Patrick Mercer

2010: H1N1 Statistical Legacy . . .

Oct 2011: Record-linkage DDW-cohort to 31 March 2009 linked to deaths

Sept 2012: PEPS Trial safety-alert

Feb 2013: Fatality in N-ALIVE Trial . . .

Year:	Epidemic or Focal-event
2009/10: Jan	**H1N1** RSS President-DH, SMB & Sir Liam
March	**Mephedrone** Patrick Mercer's PQs re CDTs
Sept	**H1N1 Scientific Advice in Emergencies** RSS evidence to S&T Inquiry
Dec	**CMO's H1N1 Statistical Legacy Group**
2011: Oct	**Mephedrone ⇔ cocaine-related deaths**
2012: Jan	**RSS Policy statement [1]**
Interim	**Survey 30 national statisticians in EU**
ONS responses	**Mercer's statistically-adept PQs**
OOPS	**DRDs** in CMO's 1st Annual Report
2013: Feb	**RSS Policy statement [2] + required actions by National Statistician & head of NHS Information Centre, Leeds**
Feb + March	**Suicides** in 2008 & 2011 . . . OOPS