Axia Research Inc.

Biomarkers and Surrogates:

Adventures at the Common Drug Review

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Background

CDR chairs have stated that surrogate outcomes are one of their biggest challenges.

There is a concern among stakeholders that the CDR questions the use of surrogates – even when these are well-accepted by clinical and regulatory communities

- contributing to higher DNL rates.

Objective (1)

Using publicly-available information:

(1) To produce a review and descriptive analysis of CDR recommendations:

- the use of biomarkers and/or surrogates
- the other characteristics of the submission
- the final recommendation.

Objective (2)

Using publicly-available information:

(2) To describe the acceptability of surrogates at various agencies:

- HTA agencies
  - CDR, NICE, PBS, SMC
- Regulatory agencies
  - HC, FDA, EMA

Methods (1)

Axia Research maintains a database of all CDR final recommendations

- current to December 31, 2010
- N = 156 (counting an indication only once in the event of resubmission).

The database tracks information on each recommendation with respect to the following characteristics:

- clinical, economic, drug, submission.

Methods (2)

All final recommendations were reviewed and the primary outcome was classified into three distinct categories:

- Surrogate (n = 68)
  - surrogate accepted (n = 40)
  - surrogate not accepted (n =28)
- Final (n = 26)
- Other (n = 62)
  - that is, clinical endpoints and scales

Methods (3)

Final outcome: end unit of health effect

- survival
- cure
- prevention of event
  - emesis, infection, pregnancy.

Methods (4)

Other: a clinical endpoint or scale

- examples of scales:
  - ACR20 (arthritis)
  - PASI (psoriasis)
  - HAM-D (depression)
- examples of endpoints:
  - exacerbations (asthma)
  - incontinence episodes (OAB)
  - disease progression (MS)

Methods (5)

Surrogate: a biomarker intended to substitute for a clinical endpoint

- HbA1C, viral load, 6MWD, BP, LDL, PFS, FEV1, IOP, biochemistry

Further classified into:

- not accepted: statement of concern or stated (other) preferred outcome
- accepted: implicit by lack of challenge

Methods (6)

We previously reported on recommendations to Dec 31 2009 (n = 138). The following characteristics were predictive of a DNL:

- statement of clinical uncertainty
- request for reconsideration
- use of price as the only economic factor
- price greater than comparators.

Therapeutic area was associated with DNL.

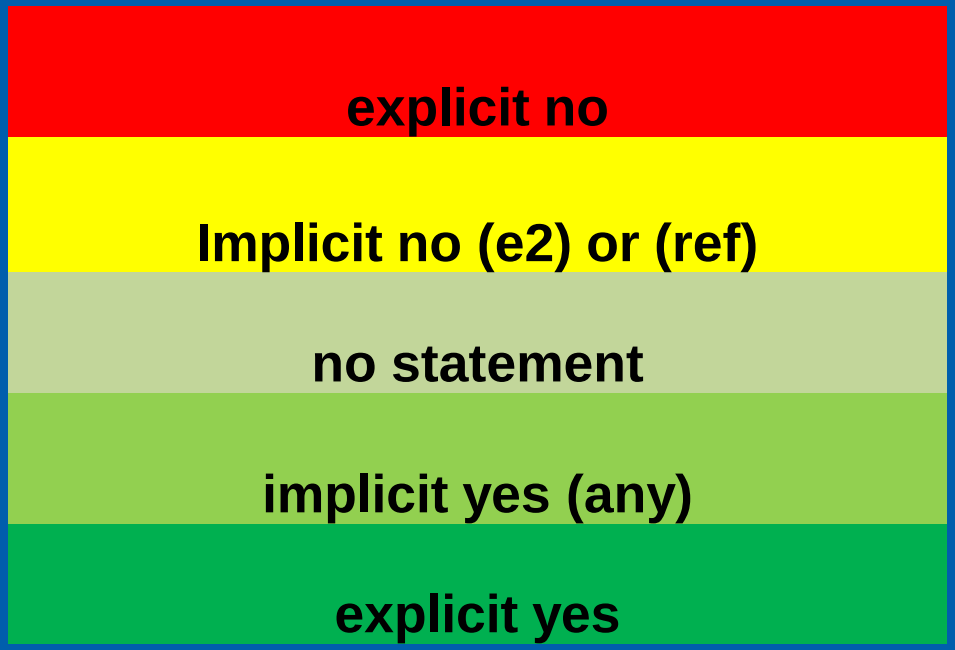
Pharmacoeconoimcs 2012; 30: 229-46.

Methods (7)

Pilot: comparing across agencies

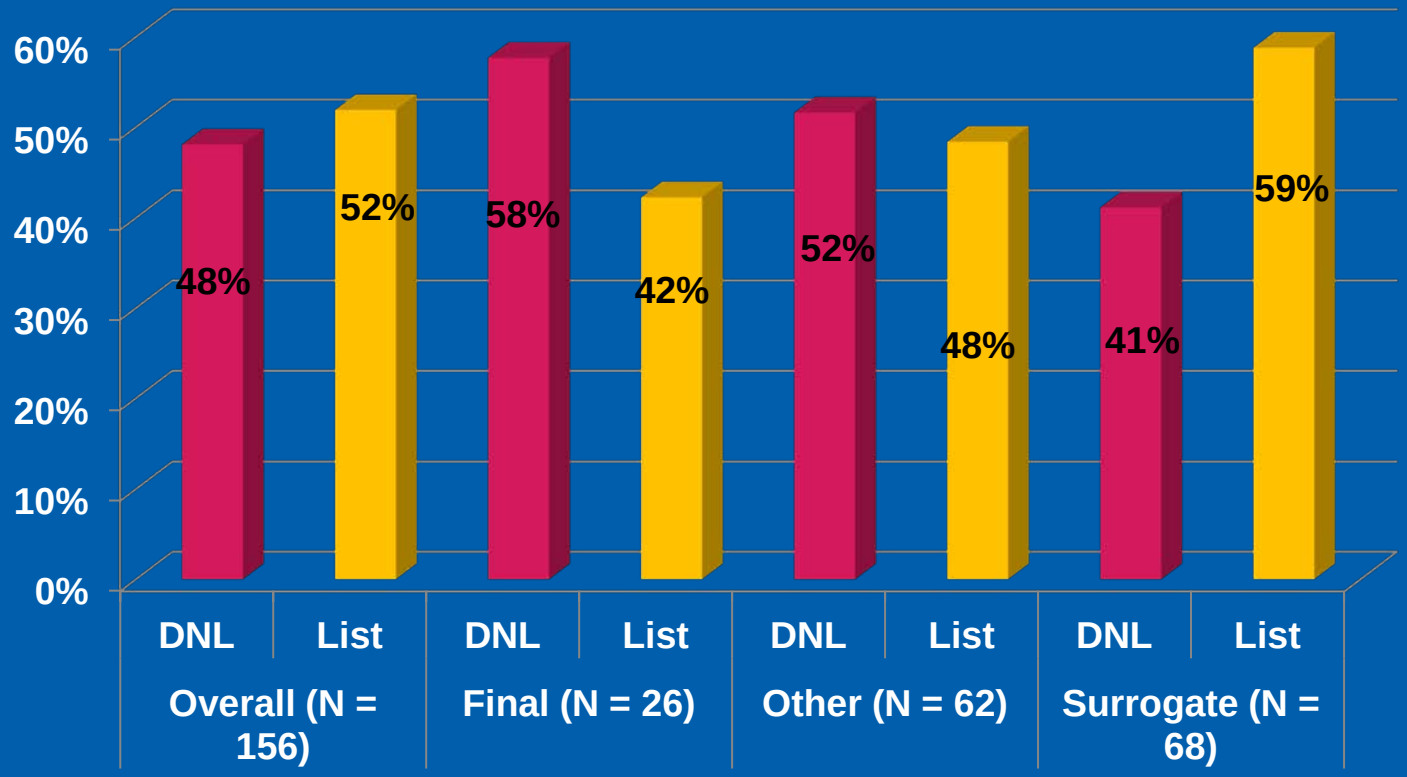
- 3 indications sampled by convenience
  - Type 2 diabetes oral drugs (T2DM)
  - Pulmonary arterial hypertension (PAH)
  - Hepatitis B + C
- reviewed and abstracted by 2 individuals
  - classified by acceptability
  - statements from any submission
    - initial or subsequent

Methods (8)


explicit no
Implicit no (e2) or (ref)
no statement
implicit yes (any)
explicit yes

Results

DNL by Type of Outcome



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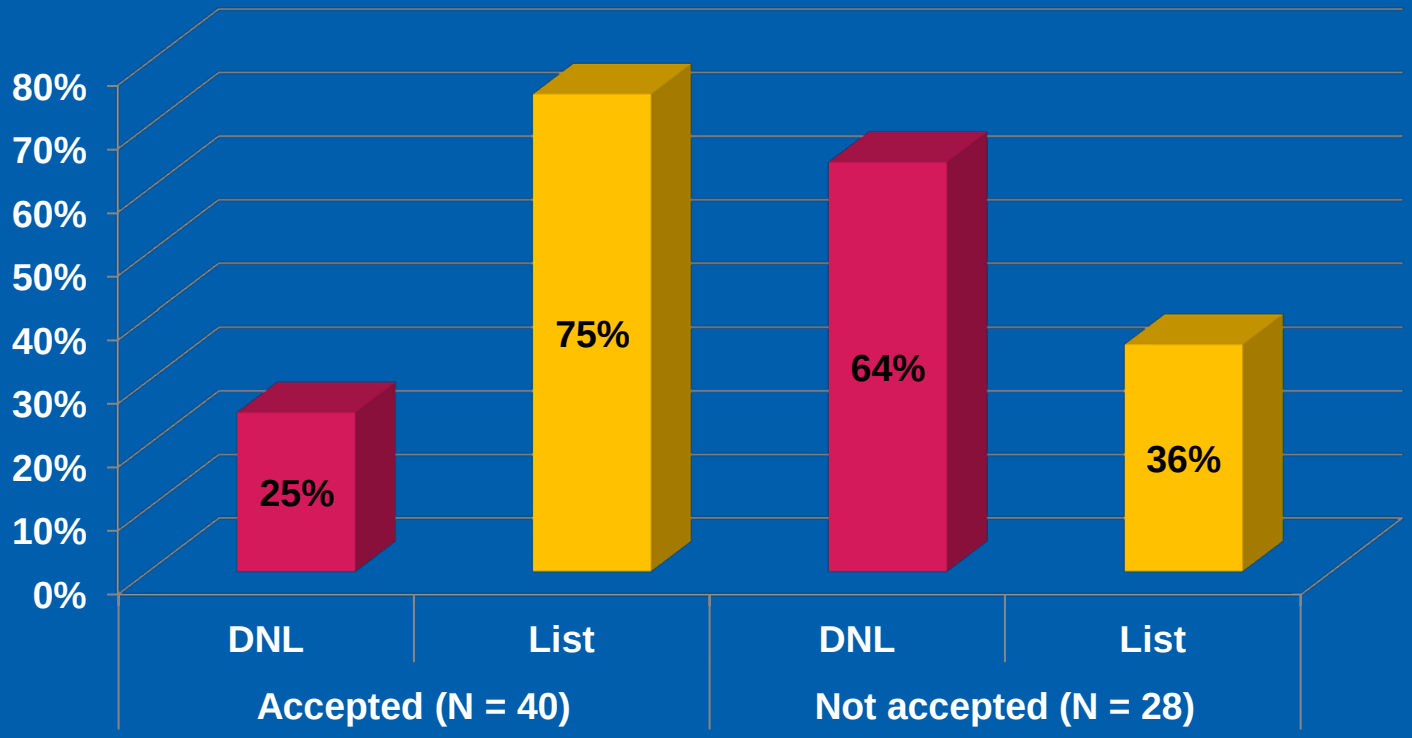
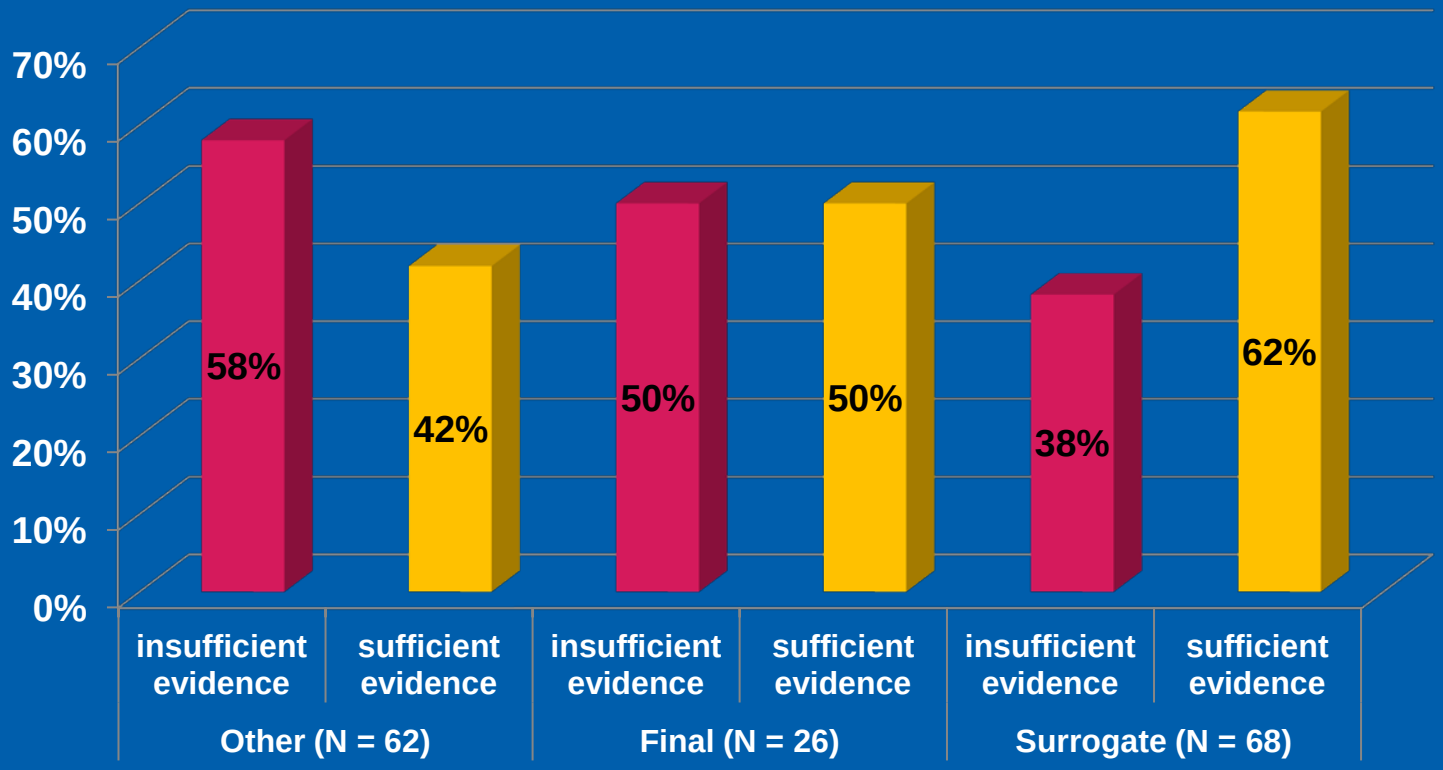
DNL by Surrogate Acceptability



Clinical Uncertainty (1)



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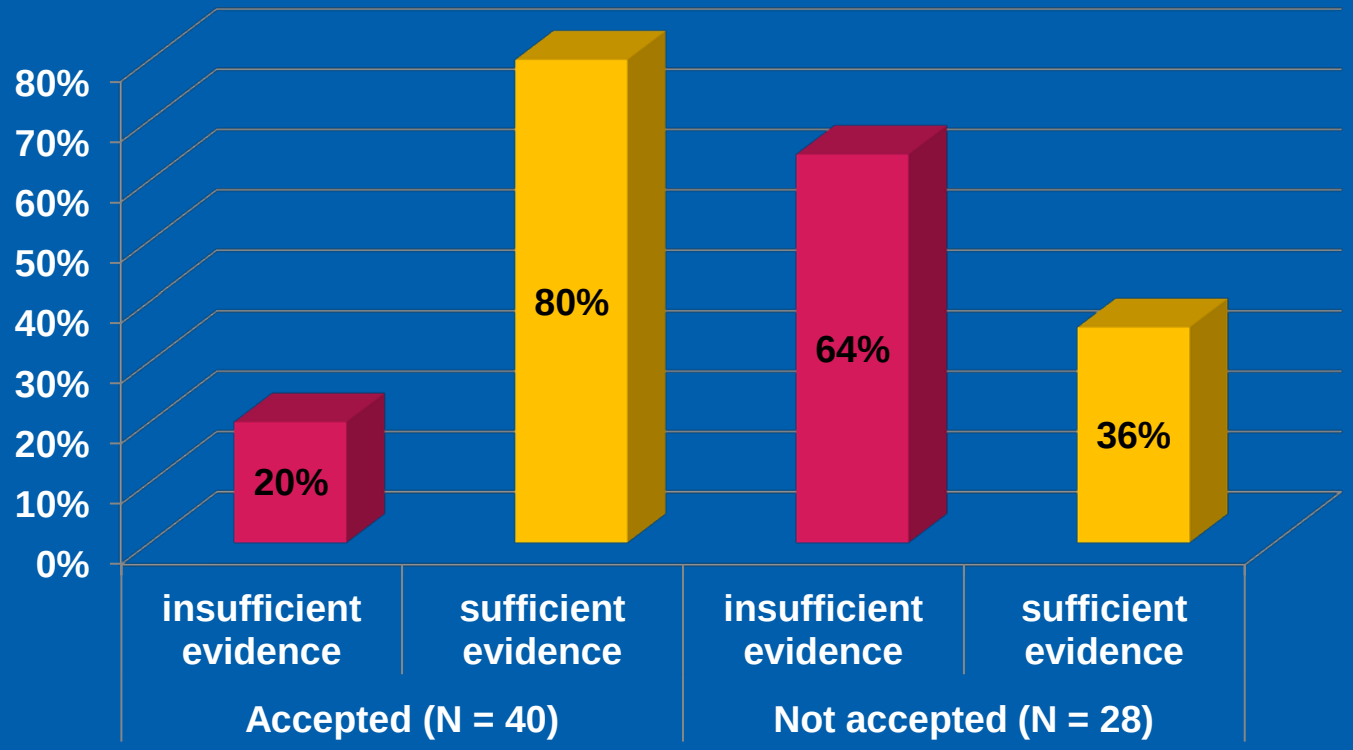
Clinical Uncertainty (2)



Economic Evidence Used

Accepted surrogates:

- 70% used only price.

Non-accepted surrogates:

- 61% considered economic models

Price

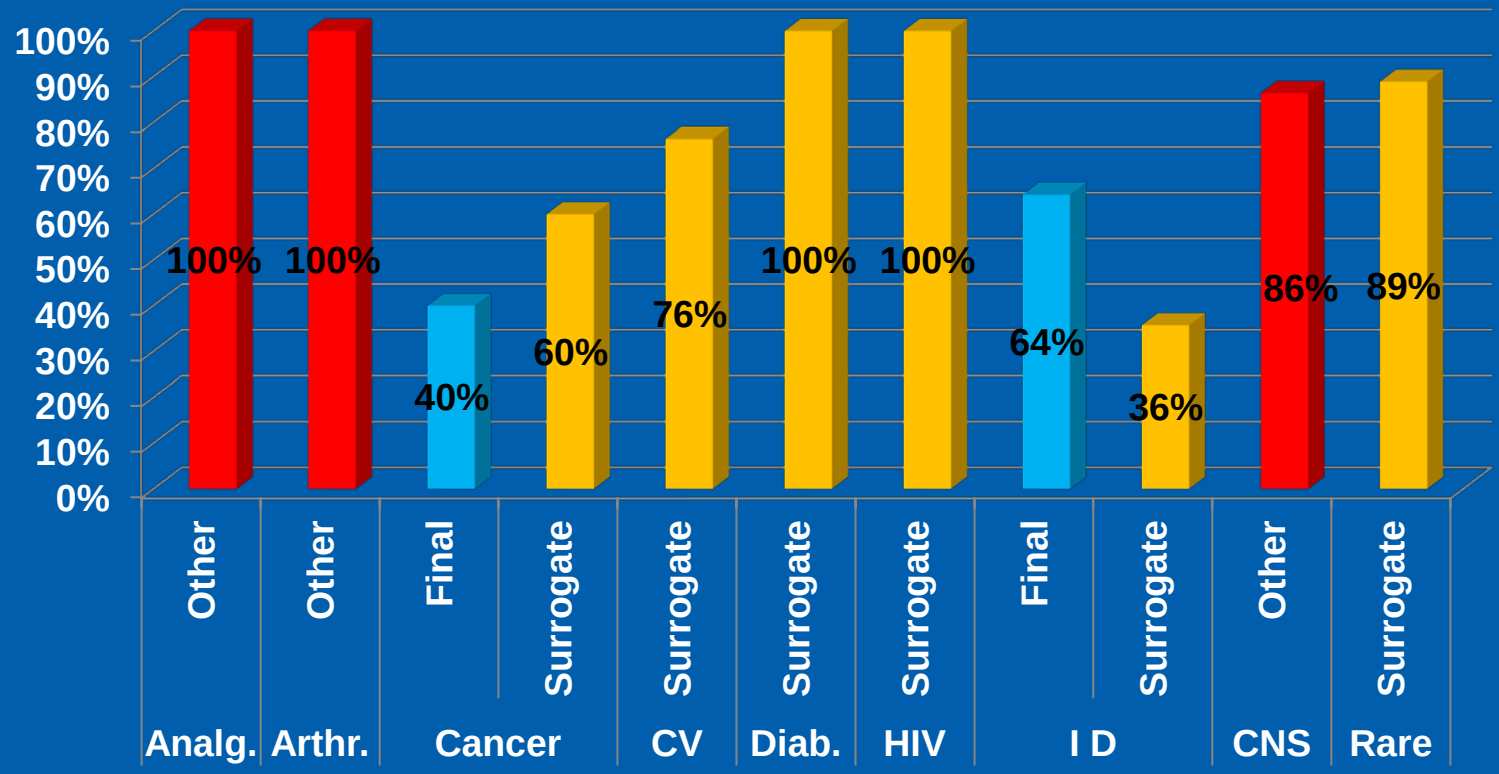
Accepted surrogates:

- 53% had same or lower price.

Non-accepted surrogates:

- 57% had price greater than comparators.

Therapeutic Area



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Other Factors

Compared to accepted surrogates, non-accepted surrogates are more likely:

- first in class (50% vs 15%)
- first for disease (18% vs 5%)
- life-threatening dx (32% vs 8%)
- priority review request (32% vs 18%).

Inconsistencies?

The same surrogate can be acceptable:

- for one disease (viral load: HIV) but not for another (Hepatitis B)
- for an existing class (HbA1c: insulins; BP: A2RAs) but not a new class (DPP-4s, direct renin inhibitors)
- for cheaper drugs (IGF-1: lanreotide) but not more expensive (pegvisomant)
- on resubmission (adefovir, sitagliptin).

Comparison by Agency

	CDR	HC	FDA	EMA	NICE	PBS	SMC
saxagliptin	no (e2)	N/S	(e) yes	yes (e1)	N/A	N/S	no (ref)
sitagliptin	no (e2)	N/S	(e) yes	N/S	N/A	N/S	no (e2)
sita/met	N/S	N/A	N/S	yes (e1)	N/A	N/A	N/S
ambrisentan	N/S	N/S	yes (used)	(e) yes	N/A	no (ref)	no (e2)
sildenafil	no (e2)	N/A	N/S	yes (used)	N/A	N/S	no (e2)
sitaxsentan	no (e2)	imp yes	N/A	(e) yes	N/A	N/S	N/A
tadalafil	no (ref)	N/A	yes (used)	no (e1)	N/A	N/S	N/A
treprostinil	no (e2)	N/A	no (e2)	N/A	N/A	N/S	N/A
adefovir	no (e1)	N/A	(e) yes	(e) yes	yes (used)	no (e1)	N/S
entecavir	N/S	N/S	yes (e2)	yes (guid)	yes (e1)	(e) yes	N/S
peg-IFN RBV	no (e1)	N/A	N/S	yes (used)	yes (used)	N/A	N/S
telbivudine	no (e2)	no (e1)	(e) yes	yes (guid)	yes (e1)	(e) yes	N/S
tenofovir	no (e1)	N/A	N/A	yes (guid)	N/S	N/S	N/S

Interpretations

CDR was the agency most likely to have a qualitative statement about surrogates, and it was largely negative (77%).

- Regulatory agencies were most likely to accept surrogates.
  - FDA 64%, EMA 83%
  - but this acceptance relied on limited indications e.g. exercise capacity

Interpretations (HTA)

HTA Agencies

- NICE had the fewest reviews (n = 5)
  - accepted 80% of surrogates.
- Other HTA agencies had few qualitative statements about surrogates
  - PBS 60%, SMC 64% ‘no statement’

Interpretations (T2DM)

OAD drugs used HbA1c.

Wide spectrum of results:

- CDR, SMC rejected surrogate based on lack of evidence (drug → final)
- FDA, EMA accepted the surrogate based on evidence linking surrogate → final.
  - ‘very well accepted surrogate’ FDA
  - ‘widely accepted outcome’ EMA
- inconsistent responses from CDR

Interpretations (PAH)

PAH drugs used 6MWD, a measure of exercise capacity.

- again, a wide spectrum of results
- regulators limited the indication to exercise capacity
- HTA agencies largely recommended these drugs for funding, despite some misgivings – even CDR.

Interpretations (Hep B+C)

Hepatitis B drugs used histology, virology and biochemistry outcomes. Hepatitis C drugs used SVR.

- these were the most challenging drugs
  - used ‘statement of concern’ to signal inconsistent statements
  - extensive debate for Hep B whether surrogates predict long-term sequelae; clinicians urged acceptance and uptake.

Limitations

There are significant limitations:

- relied on information in the public domain
  - often limited and inconsistently reported
- considerable degree of subjectivity
  - classifying outcomes by type
  - classifying surrogates by acceptability
  - may require disease expertise for improved accuracy
- descriptive analysis only.