FEATURE

CHRISTMAS 2018: LOOK BEFORE YOU LEAP

Key opinion leaders' guide to spinning a disappointing clinical trial result

Adam Hartley and colleagues present a playbook for commenting on trials with disappointing results

Adam Hartley *academic clinical fellow*¹, Mit Shah *registrar*², Alexandra N Nowbar *clinical research fellow*¹, Christopher Rajkumar *academic clinical fellow*¹, James P Howard *clinical research fellow*¹, Darrel P Francis *professor*¹

¹National Heart and Lung Institute, Imperial College London, London, UK; ²Hammersmith Hospital, Imperial College NHS Healthcare Trust, London, UK

The onward march of medical science is marred by a great deal of shuffling on the spot, since most wonderful ideas turn out to not work. To maintain a perception of an advancing tide of discovery and excitement, drug and device companies selectively promote specialty experts who can be relied on to provide an upbeat view in all situations. Internally, companies call them “key opinion leaders.”

When key opinion leaders are asked to comment on disappointing trial results in news reports or at conferences, we have observed that they seem curiously unable to recognise that the treatment doesn't work. They prefer to argue that the trial design was wrong, drawing from a set of stereotyped criticisms. Using cardiology as an example, we have systematically analysed the excuses they provide to compose the Panellists' Playbook, an anthropological classification that will be useful not only for readers but for key opinion leaders in need of inspiration (or backbone).

Compiling the playbook

We reviewed five years of reports from the world's three largest cardiology annual scientific congresses—European Society of Cardiology, American Heart Association, and American College of Cardiology—examining remarks made to large news organisations that maintain a database: Medscape and MedPage Today.^{1,2} These conferences each cover all of the many subspecialties of cardiology and have tens of thousands of attendees. Medscape and Medpage Today are widely read, providing comprehensive media coverage of these congresses.

We categorised a trial as having negative findings if a primary endpoint was not met. Two of us (AH and MS) independently identified the trial reports and extracted the explanations provided to journalists by key opinion leaders. We defined key

opinion leaders as specialty experts who provided quotes or statements for publication, regardless of whether they reported any current financial associations with industry. We then combined these independent analyses, resolved discrepancies, and formulated categories.

We found comments on 321 trials from the 15 international scientific congresses held during 2013 to 2017. Of these trials, 127 (40%) had negative results and received a total of 438 remarks from key opinion leaders. Excuses were provided for 108 (85%), with a mean of 2.5 published excuses for each trial. We defined an excuse as any explanation given for a trial's result other than the treatment not working. Sources for all 272 separate excuses are available in the supplementary table on bmj.com.

We identified 17 themes for the published excuses. Most themes could have more than one possible type of excuse—for example, the theme “age” could have two excuse types, “patients too young” or “patients too old.” We used the 17 themes to create 40 theoretically possible types of excuse and compiled the Panellists' Playbook, a categorisation that is useful both for us as readers and for current and future key opinion leaders.

Of the 40 theoretically possible types of excuse, 36 were used (fig 1). The most common excuse was “sample size too small,” used for 39 trials, 31% of those with negative results. This was followed by: “more studies are needed,” “study population too inclusive,” and “follow-up too short.”

Although key opinion leaders fell over themselves to criticise trials for being inadequately sized, in only one case did the person quoted provide a calculation for the correct sample size.³ It is not clear whether in the other 38/39 (97%) of cases the experts were reluctant to divulge the fruits of their 30 seconds

of calculation or that the excuse was simply the first thing that came into their head.

We considered some excuses vacuous and categorised them under excuse theme “V” to avoid dignifying them with a numeral. For example, the uninformative, “more studies are needed,” offered for one fifth of negative trials, suggests to us that the key opinion leader simply does not like the result and wants another throw of the dice.

Practical applications

The Panellists’ Playbook provides a comprehensive approach to summarising, or even generating, cheery key opinion leader remarks in the face of disappointing results. With the help of the playbook, no intervention is too ineffective for an excuse.

Medical journalists often contact key opinion leaders for comment with short deadlines. Key opinion leaders generally feel responsible for helping exaggerate the perceived efficacy of the specialty’s interventions; indeed, their cohort is the result of decades of relentless selection for this predisposition rather than a track record of prompt, clear, and dispassionate analysis of scientific data. Even if they lack the time, inclination, or ability to think deeply about the trial, they can pluck items from the Panellist’s Playbook to provide an effortless veneer of insight.

In principle, some of the excuses reported could be correct. An intervention may theoretically be neutral or harmful in the patient group tested but beneficial in another. However, industry does not spend tens of millions of dollars without carefully choosing the characteristics of participants. If despite all that

expertise, expense, and effort an intervention did not work, as individual physicians we should not delude ourselves that we can somehow select patients better. It is easy to slip into the belief that personal clinical practice is better than trials, but this is only because we lack randomisation, allocation concealment, and (most importantly) blinding of outcome assessment.

Researchers planning a trial could also peruse the Panellists’ Playbook for its exhaustive list of everything that might be said to undermine the results if negative. For example, they risk being criticised for having background therapy that adheres too well to guidelines. How to avoid this is less clear, since physicians and patients participating in trials tend to be more interested in prescribing and adhering to good medical therapy than are the general population. The only fix would be to seek out doctors or patients who are not interested in good care.

The extent to which the Panellists’ Playbook will be used and whether it applies to other medical specialties is not yet clear. However, one thing is certain: more research is needed.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare, other than DPF being a failed key opinion leader.

Provenance and peer review Not commissioned; not externally peer reviewed

- 1 Cardiology news and opinion. *Medscape* <https://www.medscape.com/cardiology>.
- 2 Medical news. <https://www.medpagetoday.com/>
- 3 Wendling P. PRAGUE-18: Prasugrel, Ticagrelor equal in STEMI, but questions remain. *Medscape* 2016 Aug 30. <https://www.medscape.com/viewarticle/868142>.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

Figure

Panellist's Playbook		Frequency (%)	
1	Too small	39	(31%)
2A	Too young	0	(0%)
2B	Too old	4	(3%)
3A	Too male	3	(2%)
3B	Too female	0	(0%)
4A	Disease too advanced / severe	7	(6%)
4B	Disease too early or mild	11	(9%)
4C	Clinical status evolving too quickly at recruitment	1	(1%)
5A	Too inclusive	22	(17%)
5B	Too exclusive	7	(6%)
6A	Too many comorbidities	1	(1%)
6B	Too few comorbidities	1	(1%)
7A	Patients wrong race	4	(3%)
7B	Wrong country / continent	7	(6%)
8A	Intervention wrong drug / device	9	(7%)
8B	Intervention wrong dose / device	20	(16%)
8C	Intervention wrong manufacturer	3	(2%)
9A	Intervention given unskillfully	15	(12%)
9B	Intervention could not be directly measured	2	(2%)
9C	Wrong access route	1	(1%)
10A	Intervention too late	8	(6%)
10B	Intervention too early	1	(1%)
11A	Compliance too low	3	(2%)
11B	Compliance too high	2	(2%)
12A	Background medical therapy not good enough	0	(0%)
12B	Background medical therapy too good	15	(12%)
12C	Background therapy compliance unknown	1	(1%)
13A	Follow-up too short	21	(17%)
13B	Follow-up too long	1	(1%)
14A	Endpoint blinded	0	(0%)
14B	Endpoint unblinded	1	(1%)
14C	Endpoint too difficult to blind	1	(1%)
15A	Endpoint too subjective	7	(6%)
15B	Endpoint not subjective enough	3	(2%)
16A	Not enough subgroup analyses	6	(5%)
16B	Not enough endpoints	4	(3%)
17A	Unspecified multiple reasons	3	(2%)
17B	Unspecified need to understand procedure / drug better	6	(5%)
17C	Unspecified better patient selection needed	5	(4%)
17D	More studies needed	27	(21%)

Fig 1 Panellist's Playbook. An efficient standardised framework for busy key opinion leaders asked to comment on trials with negative results