Social Media-sourced Real-world Evidence – A Novel, Cheap, Effective Method

Synopsis
The promotion and use of medicines should be based on the evidence. Whilst prospective controlled clinical trials are the gold standard, they represent a snapshot of limited use of a healthcare intervention, even if patient-reported outcomes are included. Real-world evidence (RWE) seeks to portray outcomes when real patients in the marketplace use a medicine. The use of social media as foundation to collect real-world evidence via internet portal platforms has proven itself in studies to be a rapid, inexpensive way of assembling vast amounts of data reporting patients' real experiences of treatment, including efficacy, safety and societal impact.

Is there a perfect storm approaching the healthcare industry? Is there a confluence of the increasing costs of research and development, the difficulty of providing convincing evidence of the benefit/risk of a treatment, the political needs of regulation, the downwards pressure on pricing? The counterflow is the demand to pay for a growing and aging global population with greater expectations, the requirements of providing a greater spectrum of healthcare, and risks of patent expiry, generic substitution and biosimilars. A back-of-the-envelope calculation (if things are still done that way) might show that when the return on investment for providing the data for new medicines approaches zero, it no longer makes economic sense to conduct research.

According to a US-centric report in March 2016 of a recent analysis by the Tufts Center for the Study of Drug Development, the average cost to develop and gain marketing approval for a new drug is pegged at $2.558 billion.

The analysis, included in the May issue of the *Journal of Health Economics*, indicated that the $2.558 billion figure per approved compound is based on estimated average out-of-pocket costs of $1.395 billion and time costs (expected returns that investors forego while a drug is in development) of $1.163 billion.

When post-approval R&D costs of $312 million are included, the full, product lifecycle cost per approved drug, on average, rises to $2.870 billion, according to Tufts CSDD[1]. It is hardly surprising that the prices of innovative prescription medicines are so high. A recent report in 2014 by the US Department of Health and Human Services[2] showed that a substantial part of this cost relates to clinical studies, which typically can make or break a new product.

The prospective controlled clinical trial is the gold standard by which medicines are judged in terms of efficacy and safety. They are the basis for the evidence which is used to support a doctor's prescribing of a product, and have been the basis for promotional claims to both the healthcare professional and the patient/consumer. Inevitably, clinical trials are a snapshot in time of highly selected populations treated for typically unrepresentative short periods of their lives. They demand inclusion and exclusion criteria to sharpen the precision of the questions they ask, are typically age-restricted, and only rarely include the full supermarket trolley of treatments that a real patient might be using. Whilst drug regulators have used evidence from clinical trials as their gold standard for decisions about authorising medicines, there have been critics of this standard. One of the more vociferous critics is Ben Goldacre, and in his 2012 book, *Bad Pharma*[3], in a section headed "Test your treatment in freakishly perfect 'ideal' patients", he proposes that the patients in trials are often nothing like real patients seen by doctors in everyday clinical practice. He considers that because of stringent inclusion and exclusion criteria, it is possible to recruit the patients most likely to respond to a treatment, which may suggest that an intervention is more effective than might be experienced in real life. This is particularly important in comparative studies where a study may be trying to show that X is more effective than Y. Clearly the real situation is the one that should count.

A clinical trial typically sets out to examine outcomes, and the most important one is designated the primary outcome measure. Depending on the therapeutic indication of the product, it may be something that the patient personally experiences such as pain or shortness of breath. Many studies focus on more nebulous factors such as measuring blood pressure or serum cholesterol, which are asymptomatic. Death is a favoured outcome, but the patient only comes to benefit from it if they do not die. Current thinking is advising the addition of patient-reported outcomes where patients respond to a structured instrument, which asked them about symptoms and how they feel. If these correlate well with pharmacological activity, they have proven to be a useful surrogate endpoint. However, collection of patient-reported outcomes in trials suffers from the same shortcoming that the conclusions can only apply to the selected group of individuals who were recruited into the study and under the study limitations.

What is really needed as an adjunct to the clinical trial data is information about what happens when a medicine is being used in the real world. In the real world, patients (and also some prescribers) do not always read the instructions before throwing them away. They may not take the medicine as it was intended, and there may be any number of confounding factors that were not envisioned in the clinical trials, such as bizarre diets, use of additional alternative therapies, taking the medicines continuously for a long time, being outside the age range that was tested in clinical trials, and doctors prescribing additional medicines which were not part of the original studies. This is the basis of real-world evidence, or possibly, more appropriately, the real-world experience of using a healthcare intervention.

Real-world data includes data on:

- Outcomes (both clinical and patient-reported),
- Resource use (NHS, patient and

societal),
- Treatment pathways,
- Service models,
- Patient preference, experience, and compliance.

Some of this information already exists, in that there are health records for real patients kept by their doctors, which may be part of the general practice research database. For some chronic diseases there are registries, where the ongoing fate of patients is recorded, health providers have substantial data, and a variety of other bodies are on the receiving end of information, e.g. the MHRA yellow card is real-world data.

If the data sets contain the primary information that is sought after, e.g. safety or efficacy, then these are valuable assets, but if the patients never generate data that is collected, or the dataset is limited, then the scope of the evidence may be limited. The common factor between all of these sources is that the data are retrospective, and in order to collect the information, there has not been a structured attempt to modify any healthcare intervention: what is recorded is what happened and was experienced. As the everyday management or self-management of a condition is real rather than being part of a prospective protocol (it is accepted that treatment guidelines are essentially protocols, but by and large do not place conditions on what else patients do) it means that non-clinical aspects of the use of healthcare can be evaluated, e.g. real costs to the provider and patient, societal impact of the condition and its treatment, and overall experience considerations by the user of the products. In this way, it may be possible to provide value information to help justify pricing.

All of the formal collection of health information, either from prospective studies or retrospective real-world data, makes three big assumptions: that the patient interacts with a healthcare professional who collected information, that the conditions are not self-treated, and that no one else is influencing the treatment apart from a healthcare professional. These are pretty massive assumptions, that view the patient inside a care cocoon. What would be useful to know is what happens when the patients are not being observed? The obvious solution is to involve the patients in the information supply chain, and find a way of allowing them to tell what it is really like to be treated.

One of the mixed blessings of the internet has been health information. On the one hand, there is widespread access to high-quality contemporary information from reliable sources, e.g. NHS, university and hospital websites, official patient group websites, but these are outweighed by potential disinformation either from commercial enterprises or groups and individuals with an axe to grind[4]. Social media has added to this, and people with health problems seem more willing to air their issues and problems in virtual public rather than have a proper consultation. In the developed world, ease of access to social media is almost infinitely easier than access to professional healthcare. Patients will share their good and bad news, and competent authorities have recognised this by mandating that licence-holders should be aware of adverse events recorded in social media. Facebook has been a key player in linking social media and illness, but its seemingly unedited constructs might not seem like a logical place to put one's trust.

The converse side of the interaction between social media and patients is that it is a potential starting point to find patients who are real. According to Pew Research Center, a US-based non-partisan fact tank that informs the public about the issues, attitudes and trends shaping America and the world (sourced from the internet), just under ¾ of internet users access Facebook, and lesser numbers use other high-visibility social media sites[5].

According to Warren Knight, an "international social media speaker, author and award-winning entrepreneur and coach", in 2016 Facebook is the leading social network, with over 1.44 billion monthly active users worldwide and over 31 million in the UK alone. Facebook's demographic in the UK is fairly even with 49% male users, and 51% female. He indicates that 60% of the UK population has a Facebook account. Whilst Facebook's younger demographic seem to be looking elsewhere, they still have a strong 2.5million of 13-17 year olds using Facebook, along with 26% of users still in the 25-34 age demographic.[6]

Given that many Facebook users say that one of the main reasons for using their account is competitions and offers, it is clear that they are prepared to engage online.

A recent development in thinking has been the novel use of social media to recruit respondents to participate in real-world evidence studies of healthcare interventions. Whilst Facebook seems a first stop, there are other ways to access the users of healthcare, and it is the expectation of anyone who engages with contemporary marketing of any kind to provide an email address and possibly a (mobile) telephone number.

Potential advantages of recruiting social media users for RWE studies:

- Cheap – process is very cheap and does not need substantial incentivisation to succeed;
- Rapid – if targeted correctly can result in big data sets very quickly;
- Big numbers – cohort sizes can be massive: potentially data on 1000s of patients;
- Flexible – can adjust the selection demographics to suit the study, e.g. those who are currently using a product;
- Very convenient for patients who do not even need to leave their chair, let alone their house;
- Non-clinical data e.g. quality of life experience, societal impact on working/home life can be accumulated easily;
- Typically in an RWE study, there are no exclusion criteria.

Potential disadvantages of using social media to recruit for a RWE study:

- No control over numbers: the expected cohort may never materialise;
- Ownership of data: if a study is contemplated, this should be clearly defined at the outset;
- Responder bias – because you are using a target list with a known interest in a disease/treatment, the potential for cohort bias must be considered and made transparent in any report or data use;
- Security – need to consider data

protection for input and data output, possibility of malevolent attack on project site, and prevention of multiple entries from the same responder. Consideration should also be given to a declaration of age of the respondents and consent for their data to be collected anonymously, stored and used;

- Possible spike of adverse reaction reports for a medicine;
- The most accessible model is based on open non-comparative data, and the statistical requirements for a comparative study between treatments would make the method complicated and cumbersome;
- Depends on access to social media, and the method instantly disenfranchises those who do not have computer access, the computer illiterate, the very elderly and those too disabled to use social media.

In practice, recently a successful method for collecting real-world data using social media and similar for evaluating over-the-counter medicines has been successfully developed by Iatros Consulting with Orbital Media, and their clients, and put into practice to produce retrospective open data. The method of real-world data collection using social media is ideally suited for consumer brands where the legacy evidence for efficacy may be old, and possibly based on formal studies carried out a long time ago. It may also be suitable for non-medicinal products where there is general acceptance by consumers but little evidence to support efficacy and safety.

The key ingredient to success is planning and a structured protocol. The required endpoints and how they will be evaluated should be clearly defined, and for a medicine, ideally should be consistent with the SmPC. It is worthwhile thinking about what magnitude of response will be credible. The method is ideally suited to investigate retrospectively if the common usage of a product is inconsistent with the PIL. The questions to be answered are best phrased in a non-comparative way, e.g. not asking if a worked better than b. The endpoint should be one that can be easily understood by patients and records their experience of a product, e.g. recording blood pressure is not feasible but asking about pain relief is a realistic endpoint. Responses can be factual, e.g. age, binary, e.g. yes/no answers, response on a visual analogue scale or a Likert scale. A patient response platform is created to collect the required data, and this is piloted to check the appropriateness of language, endpoints and sensitivity of the response measurements.

The Output Data Define the Value of the Study

Collecting data from a social media platformed RWE study can happen very quickly, and rather than prevaricating over under-recruitment to a clinical trial, the opposite problem may be the case. However, a poorly conceived plan may still fail to recruit. If the studies are open, retrospective and involve no mandated intervention, it is feasible to have an interim review of outcomes to confirm that the platform model and syntax of questions and answers are functioning correctly. This may give an early idea about the key responses and if the study is not functioning correctly, the opportunity exists to prematurely stop.

Every study will have a demographic output. In contrast to clinical trials, this output gives a truer picture of who is using a medicine and how it is being used. It may also produce surprises discovering who the biggest target market is, who is recommending a product (e.g. doctor or nurse) and how long it is being used for.

When the studies are complete, a formal final report is created. This may point to the need to look at subsets of the patients. There is no stratification prospectively and thus the validity of a subset may depend on the number of patients in that subset. Typically, the cohort sizes in studies involving consumers have been in thousands, and this means that not only are any findings based on numerically representative samples, but subsets may also be sizeable. The final stages of considering the data include writing papers for publication (we have published our first study in a peer-reviewed journal[7]) and discussion of what promotional claims may be made on the basis of findings. The outputs of social media-based RWE studies have proved to be acceptable by responsible bodies as evidence for supporting claims. If the study shows something to be so, then providing the claim is accurate within the context of the study, then it should be acceptable, especially if published.

RWE studies using social media have proven to be a rapid, cheap way of conducting research, and provide data that may add to the value of promotional claims, reinforce licensed indications and patterns of use, and may also assist with price justification. If you feel the storm approaching, RWE may offer good protection for the rainy day.

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