1. Executive Summary
1.1 This submission is made in response to the committee’s call for evidence on algorithms in decision making. Due to the increasing number of analytics projects being undertaken by medical research companies, and the increasing demand for ‘real world data’ that documents usage within the clinic, the agencies that licence medicines and medical devices are likely to receive increasing numbers of applications incorporating the fruits of machine learning, neural networks and allied technologies. However, such evidence might not be easily comprehended or replicated, as regulators are accustomed to doing with classical statistical approaches, creating uncertainty that is undesirable in an area so directly linked to public health. This document summarises the potential issues surrounding this topic in the context of the Committee’s Terms of Reference.

2. Biography
2.1 I am a Neuroscientist by training, with more than a decade of experience in pharmaceutical clinical development and drug licensing. I work for the global technology and consulting firm, Accenture, with a specific focus on therapeutic and digital innovation within the life sciences. This submission is made solely in a personal capacity.

3. Introduction
3.1 In 2016, a super-computer was used to answer a thirty year old mathematical problem, evaluating almost a trillion different possibilities until it encountered one that violated the conjecture under examination (Heule et al., 2016). The answer to the original question was therefore simply 'no', however the associated proof comprised some 200 terabytes of data, equivalent to more than 50 billion books.

3.2 While an impressive feat, such methods stretch the definition of a mathematical 'proof' because no human can ever hope to read them. More importantly, the computer could only answer the question, rather than offer any deeper insight into why the answer is as it is. As we begin to apply similar computing power to the business of drug discovery and healthcare, we must decide where to set the bar in terms of accepting the results at face value.

3.3 When deciding whether or not to grant marketing authorisation, drug regulators demand both the 'whether' and the 'why'; that is, robust, empirical evidence of a medicine's efficacy and safety (as may be derived largely, but not exclusively, from clinical trial data) and understanding of the biochemical mechanisms that create those effects (the method of action).

3.4 Although advances in AI offer the tantalising prospect of computers being able to more fully understand and model biochemistry and perhaps even suggest cures for diseases, this possibility is probably some way off. More likely, we will at first see increasingly complex algorithms, generated from ever larger datasets and by ever more sophisticated machine-learning, which are good descriptors and predictors of disease and/or successful therapeutic strategies, but which are not necessarily accompanied by understanding of the underlying pathophysiology. An example are so-called 'digital biomarkers'.
4. TOR: Whether and how algorithmic decision-making can be conducted in a 'transparent' or 'accountable' way, and the scope for decisions made by an algorithm to be fully understood and challenged;

4.1 A classical (i.e. non-digital) biomarker is an observable variable, be it a molecule, a gene or a symptom, which conveys information on the status of a patient’s disease. Biomarkers in general serve multiple uses. They may be the means by which a disease is diagnosed, its severity assessed or its progression monitored; they may also be the means by which a treatment is selected, its dose titrated or its efficacy assessed (in a clinical trial, for example). Consequently, evaluating the extent to which a biomarker truly represents the underlying disease state is as important as, indeed fundamental to, evaluating the treatment itself.

4.2 Aggregation and analysis of voluminous datasets presents the opportunity to uncover new biomarkers (e.g. Kugathasen et al., 2017) or to define multidimensional 'signatures' (i.e. comprising multiple variables at once), that convey information on disease susceptibility, likelihood of progression, amenability to various treatments etc. Such algorithms may then form part of the marketing authorisation application submitted for a novel medicine, or even be proposed for use by physicians after approval (e.g. an algorithm is used to select patients for a clinical trial, and is subsequently proposed to select candidates for treatment in clinical practice).

4.3 In either case, regulators will likely need to satisfy themselves that the algorithm is both fit-for-purpose and reliable. Confirmatory analyses in general are a critical function of medicines regulators. Clinical trial data is complex and its statistical evaluation even more so. Regulators validate and challenge the statistical methodology employed by drug developers and in many cases will duplicate their analysis to verify whether they obtain the same result, or perform new and additional analyses to see whether the initial conclusion holds up under different conditions.

4.4 With many companies now pursuing analytics projects, and with emerging trends such as precision medicine, adaptive licensing and value-based pricing requiring collection and analysis of large volumes of 'real world data', it seems likely that complex algorithms will become increasing common component of marketing authorisation applications.

4.5 Given that the modern world already contains many examples of 'black box' algorithms, whose inner working we do not fully understand, we must decide to what extent we are prepared to accept such uncertainty in healthcare or drug regulation. In the financial sector, we have to ceded control and compete understanding to algorithms because the monetary gains are so obvious, yet we remain vulnerable to unpredictable anomalies such as the flash-crash.

4.6 In some circumstances, most notably drugs that operate in the difficult-to-study and less well understood central nervous system, the afore-mentioned requirement to comprehend a drug's method of action may be relaxed somewhat. That is, when presented with a compelling medical need, regulators may be satisfied with evidence that a drug works, rather than also needing to know exactly how it works.
4.7 If we are able to accept that a algorithm is valid without necessarily understanding the reasons why, it will become even more critical that the results it generates can be independently reproduced. This may prove challenging. A neural network, for example, cannot be easily replicated using standardised methodology and on a variety of different hardware/software combinations, in the manner that a classical statistical test can.

4.8 Alternatively, perhaps appropriate oversight may be obtained by detailed inspections of drug developers (or their collaborators) systems, as are already used in areas such as drug manufacturing. Although some regulations exist concerning IT infrastructure within pharma companies (Eudralex Annex 11), they are in no way geared toward validating algorithmic creation or output.

4.9 Whatever strategy is employed, the government will likely need to consider expanding the regulators' budgets, capabilities and mandate in this area, if they are to keep pace with the industry they regulate. These new demands also come at a time of general uncertainty for the area. The UK’s National Competent Authority, the MHRA, is one of the world’s foremost drug regulators, and though the possibility of its removal from the European-wide regulatory system would arguably be at least as damaging to the EU as to the UK, the agencies resources would surely come under additional strain.

5 TOR: The scope for algorithmic decision-making to eliminate, introduce or amplify biases or discrimination, and how any such bias can be detected and overcome;

5.1 Bias can be introduced via the data on which algorithms are built or trained. As already mentioned, sources that may be drawn upon include so called 'real world evidence' (i.e. that created outside the strictly controlled environment of a clinical trial, such as by healthcare providers, insurance company, or patients' own mobile devices etc), whose importance in ensuring value for money to payers such as the NHS is becoming ever more relevant.

5.2 With respect to healthcare provider records, those data that are digitised become ‘low-hanging fruit’ for use in analytics projects. However, implementation of electronic healthcare records across the UK has been slow in general and that which does exist varies markedly from one institution to another. The recently announced NHS Digital Academy is a step in the right direction, however concerns raised in the Wachter review - that the NHS will require far greater funding to achieve digitisation targets - persist. If this investment can be found, it will not only facilitate analytics programmes, but also improve efficiency and clinical outcomes in and of itself (see for example the Kings Fund Review on a Digital NHS, September 2016).

5.3 Similarly, the availability of mHealth data from consumer health apps and connected medical devices may exhibit regional variation simply because of varying availability of high speed, always-on data connections. The government has allocated additional funding for research into 5G implementation, yet the average British consumers can only access 4G services 53% of the time and the UK ranks only 54th in the world for LTE connectivity. Access to 4G is limited not only by technology but also by income, raising the possibility of poorer communities being excluded from
both data collection efforts (thus generating bias) and access to novel mobile healthcare services which may employ that data.

6 TOR: The implications of increased transparency in terms of copyright and commercial sensitivity, and protection of an individual’s data;

6.1 Much of the broader data security debates apply equally to medicines and healthcare. The GDPR, and in particular Article 89 of that regulation, is good news for scientific research, however it will be important that encryption standards are maintained if the protection it offers consumers is not to be subverted. Ostensibly the regulation will come into force prior to the UK’s exit from the EU, hence companies must consider it in their development plans, however, as with all EU legislation, early clarity on what is likely to happen beyond Brexit would benefit industry enormously.

6.2 From a commercial perspective, one area that has not yet been considered in great detail is liability. Regulators have begun to classify certain mobile health apps as medical devices subject to the EU Medical Device Directive, and they should also fall within the purview of the Product Liability Directive, however neither offers specifics in relation to putative algorithmic errors or weaknesses.

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