Which computable biomedical knowledge objects will be regulated? Results of a UK workshop discussing the regulation of knowledge libraries and software as a medical device

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POLICY ANALYSES

Learning Health Systems

Which computable biomedical knowledge objects will be regulated? Results of a UK workshop discussing the regulation of knowledge libraries and software as a medical device

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Abstract

Introduction: To understand when knowledge objects in a computable biomedical knowledge library are likely to be subject to regulation as a medical device in the United Kingdom.

Methods: A briefing paper was circulated to a multi-disciplinary group of 25 including regulators, lawyers and others with insights into device regulation. A 1-day workshop was convened to discuss questions relating to our aim. A discussion paper was drafted by lead authors and circulated to other authors for their comments and contributions.

Results: This article reports on those deliberations and describes how UK device regulators are likely to treat the different kinds of knowledge objects that may be stored in computable biomedical knowledge libraries. While our focus is the likely approach of UK regulators, our analogies and analysis will also be relevant to the approaches taken by regulators elsewhere. We include a table examining the implications for each of the four knowledge levels described by Boxwala in 2011 and propose an additional level.

Conclusions: If a knowledge object is described as directly executable for a medical purpose to provide decision support, it will generally be in scope of UK regulation as "software as a medical device." However, if the knowledge object consists of an algorithm, a ruleset, pseudocode or some other representation that is not directly executable and whose developers make no claim that it can be used for a medical purpose, it is not likely to be subject to regulation. We expect similar reasoning to be applied by regulators in other countries.

KEYWORDS
computable knowledge, knowledge libraries, learning health systems, medical device regulation, mobilising computable biomedical knowledge

1 | INTRODUCTION: BACKGROUND TO AND AIMS OF THE PROJECT

Software is increasingly used in healthcare for a wide range of medical purposes, including clinical decision support (CDS), diagnostics and risk stratification, with an aim to improve efficacy, efficiency or safety. In common with regulators in the European Union, the United States and elsewhere, there are welcome proposals from the UK Medicines and Healthcare products Regulatory Agency (MHRA) to extend the regulation of software and AI as a device,[1] so that both device developers and users have greater clarity about which products come under the new regulations and what testing, documentation, quality assurance and other process are needed to satisfy regulatory requirements. Van Norman provides a useful comparison of the EU and US medical device regulatory regimes[2]; Melvin et al consider changes to the EU regulations from a regulator's perspective[3]; and it is worth noting that the current UK approach is closely based on the EU regime, with minor differences introduced since Brexit.[4] In addition, the UK National Institute for Health and Care Excellence, NICE, has published a new iteration of its quasi-regulatory framework for the evidence requirements for digital health software,[5] and the UK Care Quality Commission CQC has undertaken work on the regulation of online health and care services[6] that rely on machine learning algorithms. The AI Regulation Service for Health and Social Care[7] is now in place to help guide medical AI product developers and users as they navigate these regulations. This is especially important as the safety standards that innovations must meet need to evolve as quickly as the technologies. In parallel with these activities to improve the quality and safety of medical software, the global Mobilizing Computable Biomedical Knowledge (MCBK) movement[8] is promoting a future vision in which the developers of apps, medical devices, clinical decision support systems (CDSS) and large language models can make use of high-quality curated third-party digital libraries of computable knowledge assembled by others using established international standards.[9,10] The principles of MCBK and methods used to develop knowledge libraries are described on the MCBK website and in other articles in this special issue. Note that these digital libraries are not software libraries[11] -though some of the knowledge objects they contain may in fact be software—see later.

This distinction between the computable biomedical knowledge in an MCBK library and the software which seeks to mobilise it into clinical practice raises several queries for guidance-producing bodies and for system developers. NICE is now investigating how to publish its guidance in granular digital format as part of NICE's strategic commitment to: "*Provide dynamic, living guideline recommendations that are useful, useable and rapidly updated.*"[12] In future, this will mean that software developers can use NICE computable guidance in apps and other tools to disseminate knowledge directly in interactive format, rather than manually translating it from guideline PDFs designed for human readers. A recent pilot project with NICE including two "collaborathons" has demonstrated the feasibility of this approach.[13] However, guidance-producing bodies such as NICE cannot take responsibility for external CDSS products that use their digital knowledge products to generate a risk score, advice or triage dialogue, and would not expect the knowledge they publish to come under the scope of MHRA regulation, unless they choose to extend their product range.

As we look towards the emergence of Learning Health Systems through which knowledge, CDSS and national data are integrated and interact alongside locally input data and localised amendments made to the system, three important new questions arise for regulators:

1. What exactly is being regulated, and what is considered normal (unregulated) publishing activity? For example, while prescribing software is regulated as a medical device, there is no MHRA regulation of medical or pharmaceutical textbooks, even those designed as structured reference works intended for use in high-risk prescribing scenarios (eg, the British National Formulary [BNF][14]), irrespective of whether these texts are in paper or electronic format. However, the MHRA is a member of the Joint Formulary Committee, which is responsible for the BNF content.[15] Equally, electronic medical reference tools (such as BMJ's Best Practice[16]) which can include a variety of scores, algorithms and calculators are not currently regulated as medical devices in their current form, with limited functionality.
2. Assuming that computable knowledge libraries will not be regulated, how will MHRA and Approved Bodies examine the quality and risks of an "empty" clinical software product without considering samples of the knowledge base upon which it relies to generate advice? This is especially important given wider concerns about access to data for machine learning and the potential to perpetuate biases.
3. How will the quality and safety of computable biomedical knowledge be promoted, and clinical risks in software that uses these knowledge objects be minimised? Self-regulation by knowledge authors and curators is one possibility, but what is the appetite and capacity for organisations such as NICE, the CQC or NHS England to take a formal role in accrediting computable knowledge assembly processes to improve their quality and safety? Note that NHS England has now absorbed NHS Digital, which was previously responsible for monitoring the clinical safety of software using information standards DCB0129 and DCB0160[17]—see table in the Appendix/. We should also remember that there are other regulators with an interest in how the knowledge base is used, for example, the Copyright Licensing Authority[18] and the UK government's Intellectual Property Office IPO.[19]

Our aim in the project described in this article is to understand when knowledge objects in a computable biomedical knowledge library are likely to be subject to regulation as a medical device in the United Kingdom. We do not cover other aspects relating to the implementation of clinical decision support as these are already very well covered, for example, in the evidence-based GUIDES checklist (van der Velde 2018)[20].

2 | METHODS

After circulating a briefing paper to invited participants, a multidisciplinary workshop was held in February 2023 at the British Computer Society London office including representatives of MHRA, NICE, the chair of the Chartered Institute of Library and Information Professionals (CILIP), the Chief Knowledge Officer at Health Education England, digital health academics, a legal academic, managers, clinicians, software developers and others to explain the background to MCBK and medical device regulation in the United Kingdom, and explore how medical device regulation might apply to computable knowledge stored in MCBK libraries.

This article resulted from a draft prepared from meeting notes and slides and was refined and extended iteratively by seeking comments and input from workshop participants. The views expressed are those of individual authors rather than the organisations from which they came.

3 | RESULTS

3.1 | Summary of UK medical software regulation principles and practice

The principles underlying medical device and software regulation are to minimise risk and maximise safety and clinical benefit, while allowing innovation where possible. However, since the number of registered medical devices far exceeds the capacity of MHRA staff (130 Devices staff before merger with Drugs Division) to investigate each device in detail in common with most medical device regulators worldwide, most UK regulation of medical devices is driven by safety signals, such as adverse event reports. The US Food and Drugs Administration (FDA) has exercised regulatory enforcement discretion with some medical software, especially for low-risk products from suppliers with a strong track record, for the same reasons.[21]

3.2 | Definitions of medical device and software

According to the UK Medical Device Regulation 2002, a medical device means "*an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application, which is intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process, or control of conception; and does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means, and includes devices intended to administer a medicinal product or which incorporate as an integral part a substance which, if used separately, would be a medicinal product and which is liable to act upon the body with action ancillary to that of the device.*"[22]

Any part of that medical device—such as embedded software—is automatically included in the device if it is supplied as part of it. However, a medical device needs to respond to user input in some way, so a printed or PDF clinical guideline or a picture of an algorithm is not a device, even if it is published to support clinicians in patient management decisions.

The phrase "Medical purpose" has a broad interpretation, meaning that devices may have a medical purpose even when they are not used in a traditional medical setting, such as apps intended for lay use. "*The medical purpose is assigned to a product by the manufacturer. The manufacturer determines through the label, the instructions for use and the promotional material related to a given device its specific medical purpose.*"[23]

Software is regulated if it is supplied as part of a medical device, that is, if it is placed on the market to support the diagnosis or treatment of disease in individual humans. So, software in an app that advises on healthy weight loss in diabetics is not regulated, but software in an app that advises on insulin dosage—even when used by a non-medical person living at home with diabetes—is regulated.

Software is described in subsequent guidelines as: "*A set of instructions that processes input data and creates output data.*"[24] Software is generally understood to be instructions for a computer that tells it to carry out specified computation, producing outputs from inputs based on defined logic. This implies that the technology-agnostic model or logic specification usually carried as the payload in an MCBK knowledge object is not software as it cannot directly compute: it merely specifies the rules that should be followed by a CDSS, medical device, chatbot, etc. (see Table 1 in Summary section). Some examples of this type of knowledge include:

- Statements of medical facts ("the usual adult dose of paracetamol is two 500 mg tablets every four hours")
- Rules linking findings with a suggested action ("If blood pressure is 140/90 mmHg on three or more occasions, consider advising weight loss then antihypertensives")
- A scoring system, such as: "Give one point each if age >60 years, total cholesterol >5 mmol/L, male gender, person is a smoker, a family history of heart disease, person is a diabetic; then advise lifestyle changes if total score is three points or more."

3.3 | Brief summary of requirements for regulated devices and device evaluation

If a product is considered to be a medical device using the criteria above, the legal "manufacturer" (see next section) must ensure that product conforms to the requirements of the UK Medical Device Regulation 2002.[22] Generally, this will require the manufacturer to: register the device with the MHRA, produce a clinical evaluation report, identify and reduce clinical risks and provide evidence that an adequate quality management system has been followed. Compliance with relevant standards such as BS EN 14971 and BS EN 62304 may assist

TABLE 1 Decision on whether different kinds of biomedical knowledge objects would be regulated as a medical device in the United Kingdom, with reasons.

Level	Type of knowledge object[a]	Definition and example	Decision: regulated or not?	Reasons for this decision
1	Unstructured text	Narrative human readable text, for example, a clinical practice guideline	Not regulated	1. Human readable text cannot be used directly in a CDSS 2. It can be used to set out policy, for education etc.
2A	Tagged fragment of narrative	Deep link to a section of a recommendation, for example, first line medication for new adult T2DM is metformin	Not regulated	1. Tagging only provides a textbook index-like function
2B	Semi-structured	Organised text, a conceptual model, for example, recommendations derived from a guideline, operational and functional requirements	Not regulated	1. Semi-structured text cannot be used directly in a CDSS
3	Structured	Software-neutral, machine-readable coded knowledge which defines all data elements using formal clinical vocabulary and logic to support a decision, for example, a logical model	Not regulated	1. Is computable knowledge but is application- and site-independent 2. Not committed for use in a CDSS: could also be used to support education, research, etc.
4	Executable	Software designed to run in a specific CDS system, based on local clinical codes, normal ranges, etc.; a directly usable representation of the knowledge	Yes, regulated	1. Is intended only for CDSS applications, becomes part of the CDSS

Abbreviations: CDS, clinical decision support; CDSS, CDS systems; T2DM, Type 2 Diabetes Mellitus.
[a]Classified using the four-layer model of Boxwala et al (2011),[25] with additional material from Mehl et al (2021)[26] and an extra layer from the authors.

manufacturers in demonstrating conformity with these requirements (see table in the Appendix/ for a description of these standards).

The clinical evaluation report needs to document device testing in a relevant context, with representative coded patient data over a period, ideally with gradual, monitored introduction of the medical device into the clinical setting in a local environment. In addition to this testing, one method to assure MHRA that medical software is safe is to operate it in "silent mode" for a period. This means routing individual coded patient data to the device and recording its advice, risk score or other output, but not communicating this output to the clinicians managing patients. The performance of the device in this "field function" testing scenario[27] can then be compared with the required minimum performance and that of the clinicians managing patients unaided. It is also recognised that sometimes the only feasible way to demonstrate the clinical effectiveness of an app may be to deploy it live in such a setting.

Device regulators accept that clinical evaluation poses a challenge for start-ups and small manufacturers, so new tools such as sandboxes and an AI airlock are being developed to lower the barrier for these manufacturers.[28]

3.4 | Who is the "manufacturer"?

Legally, each medical device can only have one "manufacturer," who is responsible for ensuring the device meets applicable standards prior to placing it on the market and throughout the product lifecycle.[22] In the case of open-source software, this could be the person or organisation that modifies the open-source software as part of a medical device (eg, for the client software to communicate with back-end servers), rather than the original creator of the open-source software. The manufacturer takes responsibility for all components of the software, including any clinical coding terminologies, value sets, intermediate classification rules, algorithms derived from machine learning and third party or open-source elements they have chosen to use. This will often include the operating system code (Windows, Android etc.), runtime environments like Java or a CQL execution engine for content from a FHIR Library resource. Open source is also often used for basic utilities like timestamps, file handling or database connections. The manufacturer will need to identify and list all of these components for regulators, and would be wise to make this list available to users, too. In the case of an electronic patient record (EPR) that embeds a risk calculation algorithm, the legal manufacturer could include the EPR developer, the researcher who developed the algorithm, or the owner of the algorithm intellectual property (IP), for example, the University that employed the researcher or a spin-out company that exploited that IP.

There is an exception to the UK Medical Devices regulation for "homebrew" devices, but this is only for devices that are completely manufactured in-house and which are used only within the manufacturers' own organisation.[29]

3.5 | Useful analogies and resulting insights for the regulation of computable knowledge

The first useful analogy is in vitro diagnosis (IVD). This consists of an "assay": a set of reagents and a measurement process such as

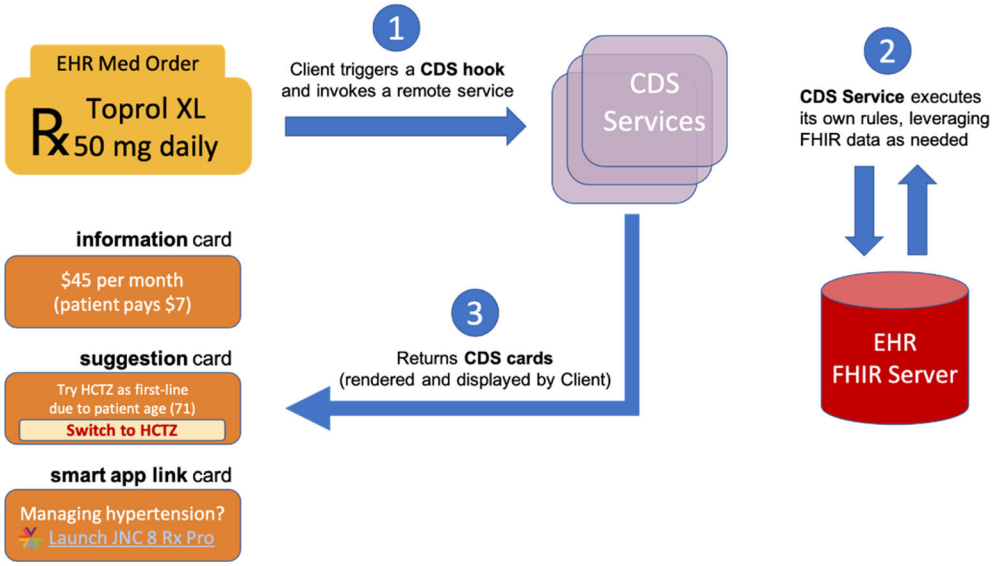


FIGURE 1 How clinical decision support (CDS) Hooks works—example of how advice is delivered following prescription of an anti-hypertensive drug, Toprol XL (from https://cds-hooks.hl7.org/[31]).

spectrophotometry that detects analytes (trace quantities of specific biochemicals, such as a hormone), without a wider intended purpose.

If an IVD is used by a laboratory to assay human blood samples to obtain results for research, it is not considered a medical device because detecting analytes is not a medical purpose. However, if a lab uses the same IVD assay in a patient group with a specific intended purpose (eg, to detect a specific condition) and then communicates the assay result to a clinician which can then influence a patient's management, the IVD is considered a device.

This analogy would only apply to a MCBK biomedical knowledge object that meets the criteria for software, that is, is directly executable. To avoid being considered a medical device, the software fragment needs to be formatted and described as purpose-neutral, that is, with no intended medical purpose. An example is the WHO SMART guidelines model[26] in which the knowledge is purpose-neutral and not intended for decision support at the individual patient level, so can be used in a wide range of settings including public health, population screening, quality assurance, education or to support research activity. Only when a specific knowledge object is described by the manufacturer as intended for medical purposes, or is requested by a CDSS or medical device such as an infusion pump to support decisions about an individual patient, does it become part of the medical device and is therefore regulated.

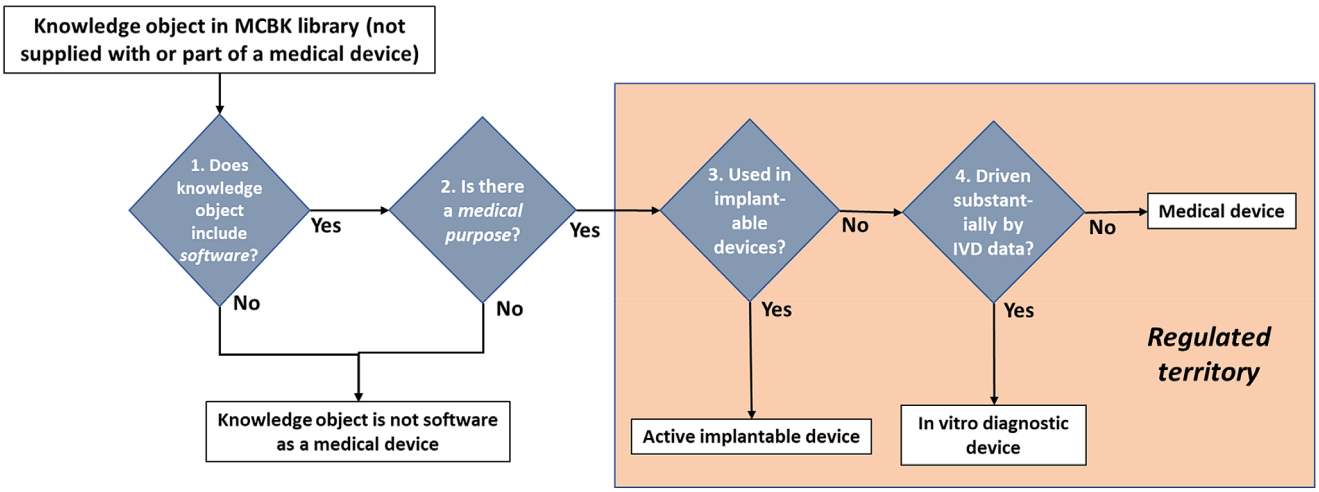
A practical example of this is the Openclinical.net website[30] that provides access to a repository of biomedical knowledge objects written by a team of researchers and clinicians, originally from Cancer Research UK, in a language called PROforma that they devised. The Openclinical platform takes the view that it is important to provide an execution environment for the PROforma knowledge objects to assist in their creation, demonstrate their execution and to allow potential users to test their performance, but indicates clearly that these knowledge objects are not for clinical use until embedded by others within a CDSS application.

An exception to that generalisation is if the library stores executable code that claims to provide a clinical function when implemented in a clinical context by a third party. An example is a Python or C++ software routine that claims to provide clinical advice in response to patient data sent from an EPR via an API such as CDS Hooks, Figure 1.[31] A CDS Hooks implementation could contain a network of entities, some of which are devices and some are not. The main clinician- or patient-facing EPR is a regulated medical device, as it has the executable logic of which events or data values are "hooks," while the remote CDS service is a device as it executes the logic and potentially queries back to the EPR to check other data values. But the CDS service may (in the future) also draw upon a CBK library of non-device logic specifications and carry out runtime translation into its own executable logic, or simply present the user with a Level 2A tagged fragment of narrative text (see Table 1).

To put it another way, if the knowledge object contains pseudocode or anything that requires translation and there is no directly applicable instruction set for translation and execution to deliver decision support, then it is not regulated. If it contains directly executable code and claims to provide a clinical function, it is regulated.

A simple calculator app and the algorithms it uses to perform addition, subtraction etc. is not a medical device unless and until it is placed on the market with medical claims, for example, it if is pre-programmed to calculate risk of cardiovascular disease, like QRisk2, or where the calculation or its result cannot be easily verified. Again, this demonstrates that software which can be used to support diagnosis or treatment decisions (eg, library database, security and search functions) is not a device unless and until it is intended for that medical purpose.

A final useful insight is that software designed and marketed for health promotion, population screening or other public health purposes is generally not considered to be a medical device as it has no medical purpose. This is because such software does not use individual person-specific data, so cannot support decision making about diagnosis or treatment at the individual patient level. "*Stand-alone software which is used to interpret or evaluate data relating to the medical care provided to an individual may be a medical device, whereas software used to analyse population data or to create generic treatment plans will not be.*"[32] However, a symptom checker app that tells a member of the public that they have a medical condition or disease or



1. *Software*: "A set of instructions that processes input data and creates output data." [MEDDEV 2.1/6 – 2016]
2. "The *medical purpose* is assigned to a product by the manufacturer. The manufacturer determines through the label, the instruction for use and the promotional material related to a given device its specific medical purpose" [MEDDEV 2. 1/1 I 1.1b]

FIGURE 2 Simplified algorithm for deciding if a clinical knowledge object in an Mobilizing Computable Biomedical Knowledge (MCBK) library is likely to be regulated in the United Kingdom and if so, which type of medical device it is. IVD, in vitro diagnosis.

one that gives them an individual percentage risk score of having a condition is defined as a medical device.[33]

3.6 | Summary of results and mapping to Boxwala's four-layer framework

To summarise this argument, we present a simplified algorithm for deciding if a clinical knowledge object in an MCBK library is likely to be regulated in the United Kingdom (Figure 2).

The two key choices are, does the knowledge object include software, and if so, is there a medical purpose. If both conditions apply, then the knowledge object is part of a regulated device. This algorithm also offers two further choices to help distinguish between the three kinds of medical devices, some of which (active implantable devices and in vitro diagnostic devices) carry more onerous obligations on the manufacturer than a simple medical device.

To put our results into a broader context, we have mapped them onto the four levels of knowledge from Boxwala et al's well-known four layer framework for disseminating knowledge[25] (see Table 1). We have split level 2 to add a new level (2A) for "tagged fragments"—meaningful elements of a narrative guideline recommendation that could be the answer to a clinical question. The openclinical.net platform mentioned earlier[30] is an example of a knowledge repository that is positioned at level 3 of this framework.

4 | CONCLUSIONS

This deliberative multi-disciplinary process has generated several useful insights, such as the analogy with IVDs, and has allowed us to make the following conclusions:

1. Regulators are unlikely to consider the biomedical knowledge stored in MCBK libraries as a medical device and regulate it, even if it relates to diagnosis and treatment, unless it takes the form of Boxwala et al's "executable knowledge," that is, software, for example, a CDSS knowledge object that responds directly to a CDS Hooks request via an HL7 FHIR API.[31]
2. Describing an object in an MCBK digital knowledge library as "suitable for medical decision support" or "will improve patient care" is unwise; instead, such knowledge objects should be presented as pluripotent, that is, providing knowledge to support a wide range of non-clinical as well as clinical tasks, such as using technology-agnostic logic to derive compliance metrics.
3. While most objects in MCBK libraries do not seem likely to be regulated, it is important to build professional and wider trust in these libraries and their contents.[34] This means adopting a standard approach to governance and quality management, perhaps through a library certification process. This also implies standard approaches to labelling the knowledge source and the intended use, and context of use, the stage of each knowledge object in the lifecycle (eg, proposed, draft for comment, validated, in use, pending withdrawal, withdrawn), as well as using standard indexing tags. This will facilitate cross library search and evaluation of knowledge objects. In addition, the library and its contents need to conform to FAIR (Findable, Accessible, Interoperable, Reusable) principles, augmented to include Traceability to the original knowledge source and Explanations, making it FAIR-TE.

Strengths of this work include that it was cross-disciplinary and engaged first hand with UK regulators such as MHRA and NICE. Weaknesses include that the approach is deliberative rather than empirical, and that we considered the position in Great Britain only, that is, England, Wales and Scotland. The position in Northern Ireland

is complicated by the legacy of EU medical devices regulations that still apply there due to the Northern Ireland Protocol. However, thanks to the global harmonisation work of the International Medical Device Regulators Forum (IMDRF) on software as a medical device,[35] regulators in other countries (such as the FDA in the United States) will follow similar principles for the definition and regulation of medical devices and software, so the insights and conclusions we outline above are likely to apply in other administrations.

A further weakness is that we do not address the acceleration of generalist medical AI (GMAI) harnessing large language models and search engines across text, images and other content. Moor et al anticipate that GMAI-enabled applications will challenge our current strategies for regulating and validating AI devices for medicine and will shift practices associated with the collection of large medical datasets.[36] In a blog on the MHRA website, author Johan Ordish has written: "*The recent advances in LLMs have rightfully raised questions about their potential use to support health and social care. As a regulator, we are excited to watch these models develop further and see their potential application in the sector.*"[37]

Further work should include testing these conclusions with other regulators, discussion with industry and software suppliers about their implications, and the development of SOPs or checklists to help quality assure knowledge objects before they are added to computable knowledge libraries. In future, we will need to consider the regulation of "off-label" uses of computable knowledge, where recommendations specific to a particular condition may be rightly or wrongly applied in situations that were not originally anticipated by the author. Finally, knowledge object developers and regulators will need to discuss the use of knowledge objects in people with multi-morbidity and how single-condition computable knowledge can be modified or "layered" for complex patients—and whether it may be possible to standardise our approaches for this.

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CONFLICT OF INTEREST STATEMENT

Jeremy Wyatt and Philip Scott co-chair the joint UK British Computer Society-Faculty of Clinical Informatics special interest group on Mobilising Computable Biomedical Knowledge. Matthew South is a founder and shareholder of Deontics Ltd. The authors declare no other commercial or other competing interests that may have affected their views or interfered with their impartiality in carrying out this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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