



## Evidence-making hepatitis C cure: Towards a science that knows more carefully

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### ABSTRACT

There has been some controversy concerning the curative potential of new treatments for hepatitis C. This follows a systematic review of the Cochrane Collaboration questioning the clinical benefits of direct-acting antivirals (DAAs). This controversy has been debated as a matter of methods regarding how best to evidence treatment in an evidence-based medicine (EBM) approach. Drawing from science and technology studies (STS), we offer an alternative perspective. We propose a different way of thinking with evidence; one which treats 'evidencing as performative'. Using the Cochrane review and its linked published responses as a resource for this analysis, we consider how hepatitis C cure is differently made-up through the knowledge-making practices performing it. We show how matters of apparent fact in evidence-based science are enacted as matters of clinical, social and ethico-political concern. We notice hepatitis C cure as a fluid object in negotiation. We highlight the limits of current debate to advocate a more critical and careful practice-based approach to knowing hepatitis C cure. This calls upon public health researchers to reflect on the performative work of their evidencing. We propose a 'more-than' EBM approach which treats 'evidence-based' science as an 'evidence-making intervention'. We consider the implications of such an approach for the evidencing of public health interventions and for treating hepatitis C in the DAA era of 'viral elimination'.

### Introduction

New pharmaceutical treatments for chronic hepatitis C evidenced to offer curative potential are having dramatic impacts. These new pharmaceuticals – known as direct-acting antiviral (DAA) treatments – are posited as offering near 100% cure of hepatitis C infection with near zero side-effects (Dore & Feld, 2015; Falade-Nwulia et al., 2017). It is for this reason, in combination with the rapid pace of their development into 'real world' delivery, that they have been presented as groundbreaking and revolutionary (Banerjee & Reddy, 2016; Gane, 2014). The promise afforded by this 'new world' of hepatitis C cure is accentuated by the marked differences of DAAs to the previous era of interferon-based treatments linked to dubious levels of effectiveness with extremely difficult to manage side-effects (Dore & Feld, 2015; Hopwood & Treloar, 2005). DAAs enact a rupture in the constitution of hepatitis C treatment. Not only do they afford the promise of cure at the level of the individual, but they make possible the promise of a future without hepatitis C. Treatments promising cure of infection potentiate, for the first time without vaccination, elimination of an infectious disease as a public health threat. This idea – of viral elimination and the end of

hepatitis C – has been enacted into global health strategy by the World Health Organization (WHO) among other actors. The WHO has promoted a number of targets to mobilise global efforts towards the elimination of hepatitis C as a public health threat by 2030 (World Health Organization, 2016b, 2016b). These targets, made possible by the promise of DAAs, shape the field of hepatitis C treatment in relation to a viral elimination future (Lancaster, Rhodes, & Rance, 2019).

Yet, there has been some controversy concerning the curative potential of new treatments for hepatitis C (Rhodes, Lancaster, Harris, & Treloar, 2019). This partly relates to a review of the Cochrane Collaboration (Jakobsen et al., 2017), also published by the *British Medical Journal* (Jakobsen, Nielsen, Koretz, & Gluud, 2018), to which there have been multiple responses (European Association for the Study of the Liver, 2017; World Hepatitis Alliance, 2017; European Liver Patients' Association (ELPA), 2017; Gastroenterological Society of Australia (GESA), 2017; Hepatitis C Coalition, 2017; Powderly, Naggie, & Kim, 2017; Foster, Agarwal, & Cramp, 2018; Cooke, Barclay, & Barnes, 2018; Barclay, Bramley, & Dillon, 2018; Koretz, Jakobsen, & View, 2018; Koretz, Jakobsen, & View, 2018; Koretz, Jakobsen, & View, 2018; Koretz, Jakobsen, & Gluud, 2018). The Cochrane review casts

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doubt on tacitly accepted knowledge in the clinical practice of hepatitis C treatment: that DAA treatments can cure individuals of their hepatitis C infection, and that such viral cure confers health benefit (Cheung et al., 2016; Simmons, Saleem, Heath, Cooke, & Hill, 2015). Based on its review of 138 randomised controlled trials (RCTs) of the clinical effects of DAAs, the Cochrane review states that there is “no evidence” to judge if DAAs reduce mortality or other liver complications from chronic hepatitis C (Jakobsen et al., 2018). This work questions the routine use of Sustained Virological Response (SVR) – the absence or near absence of virus in the blood – as a surrogate indicating clinical benefits resulting from viral cure. It is also noted that DAAs have “high costs” that are “unaffordable globally”, and that international guidelines recommend early treatment for all with chronic hepatitis C (European Association for the Study of the Liver, 2018). Against the momentum of highly profiled promise afforded by the scaling-up of DAAs to eliminate hepatitis C as a public health threat globally (World Health Organization, 2016b, 2016b), the authors of the Cochrane Collaboration use their evidence to call upon clinicians and practitioners to highlight the “uncertain clinical benefit” as well as “risks and costs” of DAAs (Jakobsen et al., 2018). They call for greater care in distinguishing between the cure of infection (indicated by surrogate markers) and the cure of disease (indicated clinically).

We do not want to take issue with the strength or otherwise of evidence produced by the Cochrane review. Others have done this (European Association for the Study of the Liver, 2017; World Hepatitis Alliance, 2017; European Liver Patients’ Association (ELPA), 2017; Gastroenterological Society of Australia (GESA), 2017; Hepatitis C Coalition, 2017; Powderly et al., 2017; Foster et al., 2018; Cooke et al., 2018; Barclay et al., 2018; Koretz et al., 2018a, 2018b, 2018c, 2018d). What we want to do is different. We want to offer a perspective from critical social science which helps think differently, and *more carefully*, about evidence related to public health intervention effects. We want to consider this moment of controversy as more than a matter of methods regarding the most optimal ways of evidencing interventions. We want to push this debate beyond matters of *epistemology* – how best to know intervention effects – to matters of *ontology* – how knowledge brings interventions and effects into being.

In the field of public health, we are much more used to thinking epistemologically. The field of evidence-based intervention is dominated by questions of method in relation to how science best knows an intervention and its effects (Sackett et al., 1996, 2000). This is an established performance with a familiar narrative, in which the RCT (and reviews of these) constitute the optimum way of knowing. The RCT is the standard against which being ‘evidence-based’ is measured (Timmermans and Berg, 2003). The Cochrane Collaboration, which produces a library of systematic and meta-analysis reviews in the field of health care, is a defining benchmark in the standardisation of evidence-based medicine (Levin, 2001; See also: [www.cochrane.org](http://www.cochrane.org)). However, we wish to think with evidence in a way which extends beyond matters of method and epistemology. Following a tradition in the field of science and technology studies (STS), we want to consider *evidencing as performative*. We want to draw attention to the performative work that evidence-making practices are doing. In contrast to evidence-based intervention approaches, we describe this as an ‘evidence-making intervention’ approach (Rhodes & Lancaster, 2019a; Rhodes, Closson, Guise, Papparini, & Strathdee, 2016). Here, we are interested in how evidence controversies – concerning the curative potential of DAAs – can be navigated. How are patients and clinicians and practitioners and scientists and policy-makers to make sense of evidence controversy? How can we generate an approach which enables dialogue across different constitutions of evidence and intervention? How can we enable an approach to evidencing which offers a more careful way of knowing?

## Performativity and matters-of-concern

The analysis we develop below draws on two main concepts: performativity; and matters-of-concern. Performativity is widely used in the social sciences and provides an alternative framework for thinking about ‘effects’ which, applied here to the field of public health, counters realist perspectives which envisage evidence, interventions and their effects as stable, knowable, pre-given entities (Butler, 2010; Mol, 2002; Race, 2018). Performativity calls into question the often taken-for-granted presumption that we can stand outside of interventions, describing them and analysing their effects. Instead, it invites us to think about these entities not as preceding their expression in implementation processes and research practices, but rather as *produced through them*. Performativity asks us to “rethink the basic ontologies with which we operate” and allows us to start “to describe a set of processes that produce ontological effects, that is, that work to bring into being certain kinds of realities” (Butler, 2010). Our interpretation of performance then, does not imply a ‘backstage’ of the ‘real’, or a central or singular performer, but envisages performance as an *enactment of reality* which emerges out of a particular set of knowledge-making practices (Law & Singleton, 2000; Michael, 2017; Mol, 2002). Importantly, we see knowledge-making practices – such as science – as at once performed and performative. There is no sense of deliberate manipulation here. Rather, this approach invites consideration of how a myriad of everyday practices – including evidence-making practices in health – work to *make things happen* (Eveline & Bacchi, 2010). This concept has been usefully applied in the field of health and drug use for instance: illuminating how legal, biomedical and methodological practices are involved in the production of stigma related to HIV (Race, 2018); drawing attention to how hepatitis C is constituted in actions which enacts patients and people who use drugs in particular ways (Fraser & Seear, 2011); and understanding how the effects of drugs and medicines vary according to the material-discursive practices producing them (Gomart, 2002; Lancaster, Seear, & Ritter, 2017; Rhodes, 2018; Dennis, 2019). In our analysis below, we use ideas of performativity to explore evidence-making practices in recent debates surrounding the clinical benefits of DAA hepatitis C treatments following the publication of a systematic review of RCTs undertaken by the Cochrane Collaboration (Jakobsen et al., 2017, 2018). We also draw on the published responses to this review (European Association for the Study of the Liver, 2017; World Hepatitis Alliance, 2017; European Liver Patients’ Association (ELPA), 2017; Gastroenterological Society of Australia (GESA), 2017; Hepatitis C Coalition, 2017; Powderly et al., 2017; Foster et al., 2018; Cooke et al., 2018; Barclay et al., 2018; Koretz et al., 2018a, 2018b, 2018c, 2018d).

Second, we draw on ideas of matters-of-concern. STS scholar, Bruno Latour, stages apparent matters-of-fact as situated matters-of-concern to make visible the social basis of objects presumed to pre-exist independently of their description (Latour, 2004). Matters-of-concern accentuates things – such as interventions and their effects – not as objective and pre-existing matters-of-fact, but as performed in practices in relation to social, material and political interests (see also: Puig de la Bellacasa, 2011). Drawing attention to how apparent universal matters-of-fact entangle with situated matters-of-concern emphasises that science is not outside the practices it evidences, but rather is inside, performative, and inseparable from, these (Latour, 2004; Puig de la Bellacasa, 2011; Stengers, 2005). We draw attention to how evidence-making in relation to the recent controversy surrounding the clinical benefits of DAAs enacts matters-fact in relation to matters-of-concern. We do this to distinguish ‘evidence-based’ from ‘evidence-making’ intervention approaches (Rhodes & Lancaster, 2019a; Rhodes et al., 2016), and drawing on the work of Isabelle Stengers (2018), call for a different and more careful way of knowing hepatitis C cure.

## Observations from a controversy

What happens when we think of evidence-making moments as matters of performance? How does this encourage us to engage with evidencing differently? And how can this help us produce evidence and intervention more carefully? Let us put the recent controversy surrounding the clinical benefits of DAAs to use in this way.

### Evidence-making uncertainty

The Cochrane systematic review performs *uncertainty*. This enactment of uncertainty is not directly derived from, or located inside, the data contained within the systematic review but is produced by how the science performs these data, including through write-up into publication. Even before the evidence is presented the published *BMJ* paper enacts uncertainty as its headline: “Uncertainties” is proffered as a topic category for the paper; and the paper is organised around the subsections of “What is the evidence of uncertainty?”, and “What should we do in light of the uncertainty?”. These headlines, taken in conjunction with the questioning title of the paper “Do DAAs cure chronic hepatitis?” make-up doubt, even before the facts of the case are assessed. Translating DAAs as an object of uncertainty is here a matter of *discursive practice*; something enacted materially in the rhetorical work of the *BMJ* publication.

The performance of uncertainty is extended further in the interpretative work contributed by the authors. They explicitly guide doctors to discuss with their patients “the uncertain long-term clinical benefit” of their DAA treatments, as well as the treatment “risks” and “costs”. This is because “patients need to know” that DAAs are not only “costly” but that there is “an absence of evidence on whether [they] cure the disease”. Uncertainty is produced through the translation of evidence from a matter of presented fact (the treatments are uncertain) to a concern in the real world (uncertainty is to be communicated to doctors and by doctors to patients). Uncertainty emerges at once as a matter-of-fact and a *matter-of-concern*.

It is the performative work of science rather than data alone that is doing the acting here. The data are but one actor in this entanglement between scientists, methods, interpretations, publications, and how these interplay in ‘real worlds’. Importantly, the data are not simply discovered, and do not speak for themselves, but are *made*. This is the case with the systematic and meta-analytic review as with any other knowledge-making event (Moreira, 2007). Here, we can appreciate that the evidence-making of uncertainty requires translational work. The evidence is not pre-existing or fixed or simply transferred but *shaped into being*, subject to how it is *put-to-use* in transformative ways (Lancaster, 2016; Moreira, 2007). At the outset then, we see that science does so much more than simply discover, for it works to translate and transform apparent facts in relation to concerns. This is a process of *qualification* (Moreira, 2007). Critically, treating evidencing as performative in this way helps attend to what might have been otherwise (Law & Singleton, 2000). Could, for instance, the same apparent ‘facts’ of inconclusive clinical benefit of DAAs have been performed differently? Might these same data have been qualified – made to matter – differently regarding their implications for patients, clinicians and practitioners? These questions invite us to explore the *social and political relations* of evidence-making practices. They orientate towards tracing how things presented as ‘matters-of-fact’ (here, discovered or proved by RCTs) are translated from, as well as into, particular ‘matters-of-concern’ (situated practices of the social and clinical).

### Matters-of-fact translated as matters-of-concern

Tracing the performative work which translates evidence into fact as context-based concerns hits home that evidence-based facts are not separable from, but entangled with, their contexts of production. One instance of this in the Cochrane review is the performance of DAA

treatment worth as “costly” and “unaffordable” (Jakobsen et al., 2017, 2018). The authors posit DAA prices as “unfair”. The evidence-making of uncertainty in relation to treatment value is not enacted by the apparent facts of the evidence reviewed alone but in how this evidence is put-to-use. The Cochrane authors say that they “do not understand the mismatch between [the] enthusiasm and the level of evidence” for the use of DAA therapy (Koretz et al., 2018a). The field of hepatitis C treatment is characterised by an atmosphere of great promise, including that fuelled by mathematical models of viral elimination potential at the population-level (Fraser, Martin, Brummer-Kornenkono, Carrieri, & Dalgard, 2018; Razavi et al., 2017). The Cochrane authors “fear that at least some of the disconnect” between enthusiasm and evidence “may reflect the influence of industry” (Koretz et al., 2018a). They distinguish between “fact” and “marketing”. Treatment uncertainty is thus performed in relation to a moral economy of fair price. This is enacted in relation to a particular concern regarding the role of the pharmaceutical industry and the different kinds of benefit that flow from treatment investment. Here, ‘benefit’ is being complicated in its performance as a multiplicity, extending beyond the clinical, as evidenced through the trials. Evidence is on-the-move, in translation. The evidence assumed to exist ‘out there’, based in the trials which establish the facts of clinical benefit, is not at all separable from the evidence produced ‘in here’, as a situated material concern (Law, 2004). The pharmaceutical industry and the “marketing” of treatment potential is enacted as a problem of evidence-based intervention. This is a *strategic move*; an evidence-making *intervention*. The lack of RCT evidence of long-term clinical benefit is being translated as an ethico-political concern regarding the “diversion of resources from other healthcare programs” (Koretz et al., 2018a), which “will negatively impact on the health of the community” (Koretz et al., 2018b).

We are therefore proposing that this is evidence-based science enacting itself as a matter-of-fact which becomes noticeable as a matter-of-concern when viewed as *performance*. In addition to tracing the performative effects of evidencing through the materials produced by the Cochrane scientists, we can also consider the published responses of those dissenting to the Cochrane review. The published responses in the *BMJ* problematise the science of the Cochrane review in multiple ways (Barclay et al., 2018; Cooke et al., 2018; Foster et al., 2018). They cast doubt on its *expertise* by locating the “discredited” and “significant methodological flaws” of the review as “lacking clinical insight and knowledge” specific to hepatitis C. They enact the Cochrane review as a *lone outsider to the mainstream* of specialist knowledge, including among “informed hepatologists, infectious disease and public health physicians”, and multiple national and international organisations. The legitimacy of such critique is performed through a long list of specialist expert signatories to the published responses. The responses further contrast the RCT evidence of the review with *alternative knowledge* on mortality and morbidity drawn from surveillance, cohorts and clinical observation, and proffer *alternative explanation* of the value of SVR as a measure of health benefit. They offer *alternative definitions of benefit* which extend beyond the clinical to encompass personal and social transformative outcomes. They position the Cochrane review as *dangerous for public health* in its undermining of the promise of DAAs to eliminate hepatitis C as a public health threat. They enact the Cochrane review as *ethically questionable*, and even “*inhuman*”, in its removal of curative potential from patients in need. They question the apparent assumption of unaffordable and unfair drug prices, alternatively casting treatment as *cost effective*. The evidence being performed in relation to EBM negotiations of hepatitis C cure extend beyond the clinical, and even the viral, to the social and political. At stake here, as previously noted (Rhodes et al., 2019), are broader matters-of-concern: *expertise* (what counts as expertise and who can claim it); *morality* (what constitutes an ethical and caring response); and *hope* (how evidence affects biomedical promise). Here, we can appreciate the Cochrane scientists and dissenters, and the materials they produce, as *entangled* actors in the making-up of evidence. Evidencing is a matter of *dialogue* in the

*negotiation of difference*, an ‘evidence’ made multiple in its particular situation.

In their response to the dissenters and their critiques, the Cochrane scientists produced rejoinders, which seek to re-assert the Cochrane review as producing matters-of-fact: “While this perspective is not popular with many people, we should not confuse opinion or marketing with fact”; “We are attempting to bring all of the facts to the table”; “At this time there is no credible evidence to support the belief that DAA treatment produces clinical benefits” (Koretz et al., 2018a, 2018b, 2018c). This defence performs evidence-based science, and in particular the RCT, as the final arbiter, reiterating the review as an exemplar of how science best knows its evidence in contrast to the “remarkably weak” alternatives characterised by “multiple biases”, “non-validated surrogate outcomes”, “computer modelling that employed treatment-favourable assumptions”, and “unproven speculations” (Koretz et al., 2018a, 2018b, 2018c). The authors’ rejoinders restate their case that it is only RCT evidence of long-term clinical outcome that constitutes certainty, absenting other forms of knowing as biased and uncertain. Locked within an epistemological dispute as to what counts as evidence (and EBM), this is a limiting and circular exchange. The dissenters retort that such narrow definitions of evidencing (epitomised in EBM) are an irrelevance, and even harm, to real-world clinical practice: “It may be that those who hold RCTs above all else still require a trial to prove that more patients with cirrhosis will die if left untreated. [...] To us such randomised trials would be unwarranted and unethical” (Barclay et al., 2018).

We can conclude that it is the *object of EBM itself* which is in the service of being performed (Lancaster, 2016; Moreira, 2007), and not only concerns regarding hepatitis C cure or the ethics of the pharmaceutical industry involvement. Moreover, attending to how research performs matters-of-concern rather than simply presenting matters-of-fact invites a more critical and careful approach to research (Stengers, 2018). As noted by Isabelle Stengers, this is because focusing on concerns rather than facts troubles the idea that “there is a single ‘right answer’” by noticing that “there are situations that concern us before they become objects of preoccupation or choice” (Stengers, 2018). The dissentions to the Cochrane review bring attention to there being ‘no single right answer’ to knowing hepatitis C cure once appreciated as matters of practice-based concern. Evidence-based facts cannot sufficiently ‘capture’ or ‘know’ situated concerns, for these extend beyond the knowability of science constituted narrowly as the mattering of facts. This points to the spiralling limits (and frustrations) of epistemological critique, which limits conversation to within narrowly defined methodological boundaries. This tells us that we need *another way to converse*. We thus move from familiar conversations about epistemological differences and which methods are best, to less predictable (but livelier) conversations about how evidence comes-to-be and is made-to-matter differently among the diverse actors involved. Treating evidencing as performance not only allows us to see EBM *working* to reproduce itself as a matter-of-fact, it also helps glimpse how certain presented facts are *worked into* selected matters-of-concern and vice versa.

### Lessons from science and technology studies

Evidence controversies bring to light the fragility of evidence-based interventions (Latour, 1987; Moreira, 2007; Whatmore, 2009). They illuminate evidencing as messy and unpredictable. The knowability of hepatitis C cure has become messier following the Cochrane review (Rhodes et al., 2019). Scientists, clinicians, expert societies and advocacy groups draw upon different forms of knowledge to evidence different realities of hepatitis C cure (European Association for the Study of the Liver, 2017; World Hepatitis Alliance, 2017; European Liver Patients’ Association (ELPA), 2017; Gastroenterological Society of Australia (GESA), 2017; Hepatitis C Coalition, 2017; Powderly et al., 2017; Foster et al., 2018; Cooke et al., 2018; Barclay et al., 2018). The

ensuing controversy risks disrupting accepted working truths in clinical and evidence-based practice as well as global strategy (World Health Organization, 2016b, 2016b). The Cochrane review can be seen to open up a taken-for-granted “virtual singularity” of hepatitis cure into a fluidity and multiplicity of negotiated less certain cures, each subject to the different knowledge claims performing them (Law, 2004; Mol, 2002).

The controversy over the effects of DAAs has been debated in purely epistemological terms regarding the best way of knowing cure. Yet this controversy (like any) is more than a question of epistemology. We see multiple versions, in fact *different objects*, of cure enacted into being through the different knowledges performing them. A lesson from the field of STS is not to neglect issues of *ontology* in evidence-making; that different knowledge-making practices do not simply contribute altered perspectives on the *same* (stable, universal) object of cure, but rather they bring into being *different* (mutable, multiple) versions of cure (Law, 2004; Mol, 2002). We can no longer hold on to the idea that there is simply one way of knowing (Stengers, 2018). Rather, we need to investigate how our different sciences do their science, how they perform multiple products, how they make-up their evidence-based medicines.

### Object lessons

In their essay entitled “Object Lessons”, Law and Singleton (2005) note that if interventions affording promise do not translate as cleanly as imagined, then the tendency is to approach this as a *technical* problem linked to research methods. The research methods are not optimum, and this is why they cannot sufficiently evidence the intervention. In this interpretation, it is not that the intervention in translation is messy but that the methods of knowing are in a mess. In the case of DAAs, the Cochrane review posits that there is insufficient evidence to properly and cleanly demonstrate, without doubt, long-term clinical effects. The dissenters to the Cochrane review claim they know the object of treatment differently, yet they cannot demonstrate this in terms which are sufficient to meet the optimum standards as defined by the Cochrane Collaboration. According to the Cochrane reviewers, without producing RCT evidence of long-term clinical effects, this intervention can never be properly known. This technical problem of messy evidence appears circular if the evidence constituted as proper and required is not technically available (such as RCTs of long-term clinical outcome).

Law and Singleton propose a second way to address the problem of messy intervention translation. This is to consider the complexity of implementation contexts as the problem which makes interventions unstable and unknowable. In this interpretation, elements of the intervention implementation – such as diagnosis, delivery and measurement – need to make better order of themselves. This implies the need for *managerial intervention*. Here, “managerialism becomes the executive tool of methodological clarity”, since “it makes a world fit for study” (Law & Singleton, 2005). The Cochrane review, for instance, positions SVR as a “flawed” device for knowing DAA effects because this surrogate has “never been validated” clinically (Koretz et al., 2018a, 2018b, 2018c, 2018d). They give pointers to tidying up varieties and measures of cure.

But there is a third way to consider. This is to *think differently about objects*, that is, the ‘things’, such as interventions, treatments and cures, that are the focus of evidencing in EBM. Law and Singleton argue that there is a “need to think more carefully about the nature of objects in the world: about what counts as an object” (Law & Singleton, 2005). They argue that we need to consider that “objects come in forms that cannot be known within the most obvious versions of commonsense”, and that “it is useful to work on different models for imagining objects”. Rather than assuming the object of intervention to be stable and clean in a messy research or delivery context – the approach to understanding the contested evidence of DAAs so far – we entertain the possibility that

our common-sense of science, our received wisdom of knowing, may limit potential for treating objects differently. We move from assumed-to-be stable intervention objects of evidence-based universal effect potential to fluid intervention objects with multiple emergent effects (De Laet & Mol, 2000; Mol, 2002).

### Fluid interventions

The object of hepatitis C cure is made noticeably fluid by its evidence controversies prompted by the Cochrane review. Controversy makes the networks producing knowledge of treatment effects more open to friction and to changes of flow (Stengers, 2005; Whatmore, 2009). As we have seen in the knowledge debates surrounding the Cochrane review, there are frictions generated between the expertise of clinicians, hepatologists, and infectious disease specialists, also pitched against generalist expertise (See also Rhodes et al., 2019). We therefore propose hepatitis C cure as an object which is both ‘becoming’ (in-the-making) and ‘fluid’ (open to transformations). The controversy evidencing hepatitis C cure offers a resource for making visible that there is no single way of knowing cure (despite such rhetorical claims being made in the name of EBM), and thus no singularity of cure (despite cure being performed in this way).

The evidence performances of the Cochrane review and its responses bring into being varied objects of cure. First there is SVR. This device performs cure in a particular way. It is used routinely in clinical practice as a surrogate of *viral cure*, also termed *viral eradication*, evidenced by the absence or near absence of virus in the blood. The Cochrane review questions whether this surrogate is necessarily indicative of viral cure, given the presence of HCV ribonucleic acid (RNA) in cells of the body despite its apparent absence in the blood. It also questions bias linked to observational studies comparing clinical outcomes between those with SVR and those without, and comparing viral cure evidenced by SVR between those treated and untreated with DAAs. It declares SVR a “flawed” surrogate (Jakobsen et al., 2018). This is because of its lack of validation in relation to long-term clinical benefits, or cure of disease, following apparent viral cure. The Cochrane authors accordingly note examples of the progression of liver disease despite undetectable HCV-RNA in the serum. This introduces a second object of cure, *cure of disease*, which may or may not be linked with surrogate markers of viral cure, and which is evidenced clinically in the short or long-term. There is also a third object of hepatitis C cure negotiated in these exchanges, and this is *viral elimination* at the level of the population, and even nation-state. This object of cure is brought into being through reference to mathematical and computer modelling projections of viral elimination following reduced transmissions linked to anticipated rates of viral cure (Fraser et al., 2018; Razavi et al., 2017; Rhodes & Lancaster, 2019b), and is also materialised in viral elimination targets (Lancaster et al., 2019). All of these cures are made-to-matter differently according to how they come to be known in situated practices. Whereas the fluidity of intervention goes largely unnoticed in EBM given overriding technical concerns oriented to isolating and replicating universal intervention effect, we need an approach which engages across different knowledge-making practices (including beyond science) to allow for multiple cures to matter.

### Knowing cure, and making evidence, more carefully

Let us move towards some conclusions. We have proposed treating science and other forms of evidencing as performative practices. This approach, we have argued, helps appreciate how evidence-based interventions incorporate universalised matters-of-fact with situated matters-of-concern. Accordingly, this helps notice how interventions are not separate from, but entangled with, everyday clinical and social practices. Thinking of scientific, clinical and other evidence-making practices as performative is a strategic intervention which has practical and political implications. It transforms the terms of the debate, opens

up multiple possibilities, and allows us to know the object(s) of hepatitis C cure more carefully (in ways that matter). As Buter (1990: viii) has argued, “[o]ne might wonder what use ‘opening up possibilities’ finally is, but no one who has understood what it is to live in the social world as what is ‘impossible,’ illegible, unrealisable, unreal, and illegitimate is likely to pose that question.”

### A more careful science

Attending to evidence-making as a performative practice is a more careful way of knowing. It helps reassemble evidencing in particular social, political and ethical concerns. We can no longer act *as if* EBM produces clean facts isolatable from their knowledge-making practices and contexts. The ‘facts’ that are made in evidence-based science, how they are put-to-use, and how they are made-to-matter, is accomplished through performance work that is at once affected by, while affecting, its social relations. A more careful evidence-based science does not simply ask ‘What is the evidence?’, but also asks ‘How is evidence made?’, ‘How is evidence put-to-use?’, and ‘How is evidence made-to-matter?’ (Rhodes & Lancaster, 2019a). These questions, we suggest, are not merely troublesome but a “vital necessity” (Puig de la Bellacasa, 2011) if our goal is to improve implementation outcomes in health which contribute to making more liveable worlds. A more careful science attuned to matters-of-concern is at once a more *caring* science attuned to matters-of-care (Puig de la Bellacasa, 2011).

In the case of treating hepatitis C, the question for a more careful science is therefore not only “Do direct-acting antivirals cure chronic hepatitis C?”, as posed by the Cochrane review published in the *BMJ*, but “How are direct-acting antivirals performed to *make* a cure for chronic hepatitis C?”. The first version is EBM as we know it. Here, the object of cure is located inside the make-up of DAAs. It is an essence that DAAs either have or not, and it is the function of science to evidence this presence or absence. The second version is a more careful science of evidence-making. Here, the object of cure is located inside the knowledge-making practices which produce it, and the function of science is also to investigate this knowledge production. In the second version of science, multiple and mutable cures become noticeable, as different cures become absent or present subject to their evolving knowledge-making practices.

A science which treats evidencing as performative and interventions as emergent is useful precisely because it investigates beyond the virtual singularity of EBM. It allows into the mix, for instance, the variants of treated hepatitis C which co-exist and matter in practice according to the situated concerns of clinicians, patients and advocacy groups otherwise side-lined by the version of EBM performed through the Cochrane review. This affords a science that is much more critically attuned to evidence-making as an *intervention* because it is noticing what evidence-making *does* in practice and how this affords *care*. Rather than treating evidence controversies as technical methodological problems in need purification or clean-up (Latour & Woolgar, 1986), it is an approach which helps “reclaim” (Stengers, 2018), by *working-with* rather than against the mess and complexity which is so often evident in public health practice but masked by normative (limiting) ways of practising EBM.

### A more careful viral elimination science

One more careful way of knowing hepatitis C cure brought to light by the Cochrane controversy concerns the performance of ‘viral elimination’. As we have indicated, the *BMJ* published debates enact an ontological disturbance in the knowing of hepatitis C cure, with variable objects of cure (and care) oscillating for attention, including: viral cure/eradication; cure of disease/recovery; and viral elimination (Barclay et al., 2018; Cooke et al., 2018; Foster et al., 2018; Jakobsen et al., 2018; Koretz et al., 2018a, 2018b, 2018c, 2018d). These debates might afford an *emerging carefulness* in how cure comes to be known as

well as measured, for instance, through surrogate markers, clinical outcomes, observational and surveillance indicators, patient experiences, and other materials. A more careful science involves *dialogue* across different forms of knowledge and knowledge actor, and is thus a more *considered* science. This strikes us as particularly apposite in a period characterised by high speed and ground breaking pharmaceutical treatment developments which enact promise not only of individual cure but of global viral elimination.

Multiple forms of evidence entangle to perform an imagined future of hepatitis C viral elimination, including global elimination targets, mathematical modelling projections, local accounts of viral elimination intervening, and strategies and policies of nation-states 'signed-up' to global elimination goals (Lancaster et al., 2019; Rhodes & Lancaster, 2019b). Viral elimination potential is an evidence-making performance. This is not to say that viral elimination potential is not real, or that a future without hepatitis C is not possible, or that some ways of knowing viral elimination might claim greater epistemological veracity than others. Rather, it draws attention to how a more careful elimination science is attuned to knowing how viral elimination is variably made-up in its evidencing practices and how this making-up is situated in relation to particular social, political, economic and policy concerns. There is the virtual singular of viral elimination performed as a matter-of-fact – this is the viral elimination we see performed most often – and there is a messier, complex, less stable, more fluid, 'viral elimination multiple' which is performed as local matters-of-concern. We can trace how the performative work in some of the responses to the Cochrane review seeks to preserve the purity of the singular virtual of viral elimination (European Association for the Study of the Liver, 2017; World Hepatitis Alliance, 2017; European Liver Patients' Association (ELPA), 2017; Gastroenterological Society of Australia (GESA), 2017; Hepatitis C Coalition, 2017; Powderly et al., 2017; Foster et al., 2018; Cooke et al., 2018; Barclay et al., 2018). While the Cochrane controversy concerning DAAs is relatively narrow in its field of focus, perhaps even esoteric to some, and possibly short-lived, it prompts us to propose that a more careful viral elimination science is warranted.

### Conclusions: towards evidence-making intervention approaches

A more careful science extends beyond that restricted to matters of epistemological concern. We are advocating a way of knowing health intervention that is *more than* epistemological and *more than* a matter-of-fact. We should not proceed as *if* science is separate from its implementation practices and matters-of-concern, and we need *more than* a single way of knowing. Following Isabelle Stengers (2018), "another science is possible". She writes: "The essential thing with 'matters-of-concern' is to get rid of the idea that there is a single 'right answer', and instead put what are often difficult choices on the table, necessitating a process of hesitation, concentration and attentive scrutiny" (2018: 3–4).

Stengers (2018) is advocating a science that incorporates multiple forms of knowledge-making, including those beyond evidence-based science as we know it. This invites a new set of relations between scientists, experts, clinicians and, indeed, the communities they serve. In this version of science, uncertainty produced through evidence controversy is *productive*, for it generates a critical hesitancy and reflection which enables science (and clinical practices) to perform as concerns in ways that are made-to-matter. It requires that scientists and clinical practitioners share their knowledge without pre-empting how it should be taken into account. This is a more careful reflexive science than the 'faster' sciences reproducing matters-of-fact. In this more careful way of knowing "what is messy is not defective" – a technical problem of research method to erase before facts become possible – but a material concern that we can "learn to live with and think with" (Stengers, 2018). This forces us all – as researchers, experts, practitioners, patients – to transform the terms of the debate, expose the consequences of different ways of thinking, preclude shortcuts, and give voice to the hard questions faced in policy and practice, especially in times of rapid

biomedical innovation. As the DAA debates illustrate, simply dismissing certain concerns as 'non-scientific' is insufficient. The limited lexicon of EBM to which proponents and opponents appeal restricts the terms of the debate without finding ground for engagement. An evidence-making intervention approach seeks to enable evidence-making relations that give space for dialogue and voice to diverse matters-of-concern. Rather than "systematically downplay[ing] anything that doesn't directly contribute to the cause of advancing specialised knowledge", specialists need space to "take seriously the matters-of-concern arising from the innovations they promote" (Stengers, 2018). We are no longer talking about evidence *and* intervention, or fact *and* concern, as if these can be isolated from one another, but evidencing *as* intervention, and intervention *as* mattering in relation to practice-based concerns.

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