Open Source Malaria Entry for the Cochrane REWARD Prize

*1) Describe the initiative and how it has addressed research waste in at least one of the 5 stages of research (questions, design, conduct, publication, reporting) in the area of health*

Open Source Malaria (OSM) aims to discover and develop new medicines for the treatment of malaria through an open source research model that eliminates research secrecy and duplication of effort. The consortium operates according to a set of Six Laws, the most important of which are: i) all data and ideas are freely shared; ii) anyone may take part at any level; and iii) there will be no patents.1

The consortium, founded in 2012, has operated with a modestly funded core of one full-time researcher supported by the Australian government and an NGO (the Medicines for Malaria Venture, Geneva). This core leverages considerable in-kind contribution from the wider community: to date more than 300 people have participated in various ways, from strategic advice and technical expertise to the physical preparation and testing of drug candidates.

To date, four series of antimalarials have been evaluated. The first showed promise, but was parked because of insuperable roadblocks. While currently shelved, the work was published and all data is publically available.2 Series 2 was abandoned when it was discovered that another group was working on it in secret. Series 3 is undergoing basic studies to identify its molecular mechanism of action. Series 4 has been extensively evaluated because of its exceptional promise: the constituent molecules are able to cure mice of a model of malaria. Series 4 is positioned to potentially achieve a world first, the nomination of a molecule from an open source project entering clinical trials.

OSM reduces research waste in the following ways. Examples are provided under Question 2.

**a) Conduct.**

The most important way in which OSM reduces research waste is by avoiding unnecessary duplication of effort. Everything is in the public domain in real time, including experimental failures, inactive molecules and undesirable outcomes.

**b) Reporting.**

Transparency, by reporting research, online and in real-time, means that all onlookers know what each member of OSM is doing, and if work is contributed it is because that contributor knows that that work is currently needed. The knock-on effect is that follow-on contributions may be made spontaneously by highly qualified individuals from anywhere in the world.

**c) Questions**

The direction of the research consortium is openly debated, on a democratized platform where seasoned pharmaceutical professionals are able to interact with junior students. Debate and research occur simultaneously, thereby *enabling efficient changes in research focus*.

**d) Design**

The technical platform uses existing online infrastructure3,4 that allows for the widest number of people to participate, and builds/promotes open standards wherever possible. Future improvements are constantly being sought, as part of the discussion, so that others from outlying disciplines (*e.g.,* software development) can contribute.

**e) Publication**

OSM publishes its work in both open access journals and other publicly accessible media in order to ensure full data availability for all participants. Research papers are openly and collaboratively written to allow authorship by anyone. The papers themselves make clear what the community can do next to advance the science quickly.

*2) Describe any (pilot) data showing how the initiative has lowered research waste.*

Further to the above, specific examples of how OSM has lowered research waste are as follows:

**a) Conduct**

Biomedical research is expensive, of both resources and peoples’ time. All drug candidates in OSM are shared openly, along with their biological efficacy, so it is clear to everyone which molecules are worth pursuing and which are not. This model of research prevents wasteful duplication of effort (where two or more people work on the same task at the same time) and means that all of the raw data produced by the project will be available for use by anyone and forever.

1. In 2017 in OSM Series 4, a required modification to the molecule was undertaken by a team in the US, who clearly showed the modification was deleterious, saving time and effort of other teams. A group of students in Brisbane is now modifying a single atom of the molecules made by the US team to see if this regains biological activity.
2. Student crowdsourcing has been undertaken extensively (Australia, UK, US). Research waste is reduced by students generating outputs being used in a real-world project, rather than a generic lab where they would be discarded. Furthermore, students are more highly engaged in their education due to the broader connections they are achieving.
3. Spontaneous contributions are not limited to academia. The most promising-looking molecule in Series 4 has been contributed by a leading research group in the company Pfizer (USA), who are providing their time and expertise freely because they recognize the potential impact.
4. Duplication of effort is avoided by eliminating work being performed behind closed doors, as happened with OSM’s Series 2. Work ceased when it became known another team was looking at similar molecules and resources were efficiently reallocated.
5. OSM is decentralized andthe team expands and contracts as needed. There is no inflexible infrastructure cost (*e.g.,* a dedicated building) and people are not contractually locked in, leading to low transaction costs.

**b) Reporting**

Open, online laboratory records kept by OSM contributors contain machine-readable strings that allow for maximal discoverability through search. The physical samples created by contributors are freely available for others to test *vs.* other pathogens, as has already happened *vs*. tuberculosis, other bacteria and fungi.

**c) Questions**

The continual process of peer review at the heart of OSM lowers research waste by making it less likely that unproductive research lines will be pursued. In Series 1, a significant debate around a potential molecular liability started spontaneously following a comment from a world expert in the field. The debate was subsequently recorded on YouTube and eventually led to research effort on the series being scaled back, thereby saving time and considerable resources. Peer review has also saved resources when it has been noted that a molecule currently being planned for synthesis can instead be purchased cheaply.

**d) Design**

The technical and infrastructure needs of OSM are continuously debated. It would be more efficient for the platform to “perceive” the molecule a scientist is working on and automatically connect that person to other scientists working on that same molecule. This need has already been discussed, planned and proposed in a published research paper that can now serve as a proposal for funds.5

**e) Publication**

The paper describing Series 1 was published alongside a considerable volume of supporting data and compressed versions of laboratory notebooks, all of which can be browsed, searched, and reused. The current writing of a paper on Series 4 has involved assigning tasks to contributors, allowing federated contributions from everyone, and employing Github as a public filesharing system.6 This increases efficiency by allowing continual peer review during writing and the rapid identification of weaknesses in the paper.

*3) Describe how the initiative might potentially be scaled up*

a) *A Broader Movement*. OSM has contributed significant evidence that there is major social enthusiasm and support for approaches to new medicines that are transparent and distributed. Scale-up requires more funding of the project core, which will allow more contributions from the community to be folded in to a unified project output. Greater funding to the project core requires clarity on the economics of whether an open source medicine can make it to market, which has still yet to happen. To devise a route to this precedent, a broader *open source pharma* movement has been created (of which OSM is a part) to explore new ways of creating a scaled-up model that is able to compete with the traditional pharmaceutical industry.7 One of the possibilities is to make use of market exclusivity (granted to new medicines) to allow investments to be recouped before a medicine goes generic; using market exclusivity would be compatible with complete transparency in the R&D.

With increased core funding comes a better marshaling of community resources through a matrix of mentors and mentees, along with retention of contributors’ freedom to act. Such systems have been seen in software development, where core industry funding has led to large-scale open source software projects delivering market-leading products (*e.g.,* Google core funding of the Chrome open source community).

b) *Welcoming of Others*. OSM is covered by the Creative Commons CC-BY license, meaning everything it generates may be used by anyone else for any purpose, including making money, provided the consortium is appropriately cited. This retains the widest possible use and discoverability of the discoveries while maintaining the possibility of a commercial body taking a discovery through to market.

4) *Provide a justified estimate of the potential reduction in research waste that the initiative might achieve.*

Ironically, an exemplar of avoiding research waste would come if an open source series failed in development. Lessons would be learned by all participants regarding why the series failed, and how such a failure could be avoided in the future. If OSM led to one such series failing in Phase 2 of an antimalarial drug development program (which costs roughly $40M from start to finish), this would represent a saving to others of ca. $20M, depending on the timing and nature of the failure.

Related to this are open source drug development programs that are “shelved” and then archived, awaiting possible resumption by others. Since all the project data are in the public domain (containing far more detail than is ever found in a traditional academic publication), a series may be resumed, or added to, by anyone as though they were project insiders. This avoids future scientists needing to repeat the mistakes of others. There is great potential in the future for open source consortia to act as a repository of parked projects from the pharma industry in this way, particularly where the pharma companies have closed due to financial pressures, leading to enormous losses of intellectual capital (*e.g.,* AstraZeneca closure in Bangalore). Retaining one pharma series fully in the public domain would save others repetition costs of *ca*. $3M per series.

Most of the research waste that is avoided however, is *via* the execution of efficient, non-duplicative research. This is challenging to quantify because it is highly granular, with manysmall savings across a spectrum of projects longitudinally over time as described above: avoiding duplication, drawing in highly skilled individuals, sharing resources.

**References**

1) Open Source Malaria: opensourcemalaria.org, accessed May 11th 2018.

2) Open Source Drug Discovery: Highly Potent Antimalarial Compounds Derived from the Tres Cantos Arylpyrroles, A. E. Williamson, et al. *ACS Cent. Sci.* **2016**, *2*, 687–701. DOI: 10.1021/acscentsci.6b00086

3) Experiences with LabTrove, a Researcher-centric ELN, K. A. Badiola et al. *Chem. Sci.* **2015**, *6*, 1614-1629. DOI: 10.1039/C4SC02128B

4) Open Source Drug Discovery – A Limited Tutorial, M. N. Robertson et al. *Parasitology* **2014**, *141*, 148-157. DOI: 10.1017/S0031182013001121

5) SCINDR - The SCience INtroDuction Robot that will Connect Open Scientists, C. Smith, M. H. Todd, L. Patiny, C. Swain, C. Southan, A. E. Williamson and A. Clark, *Research Ideas and Outcomes* **2016**, 2:e9995. DOI: 10.3897/rio.2.e9995

6) Github About: <https://github.com/about>, accesed May 11th 2018.

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**Supporting Items**

1. Article in The Conversation (Sept 14th 2016) entitled “*Making drug development less secretive could lead to quicker, cheaper therapies*” by Professor Todd and Dr Alice Williamson, accompanying the publication of OSM’s first paper (PDF attached).
2. Video of Conference Presentation at Linux.conf.au (January 2018) by Professor Todd entitled “Open Source Pharma” about the Open Source Malaria consortium: <https://www.youtube.com/watch?v=VBodnd68iwU>
3. Article in the Guardian (19th April 2017) entitled “Why Open Source Pharma is the Path to Both New and Cheaper Medicines”
4. Article in the Guardian (1st Dec 2016) detailing the use of OSM in a crowdsourced project in which school students made samples of the expensive drug, Daraprim