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 by adopting an open source research model, in which there is no secrecy in the research. 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 modest 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 through to physical samples of drug candidates.

To date four series of antimalarials have been evaluated. The first showed promise, but was parked because of (currently) insuperable roadblocks; the work was published.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. This 4th series has the best chance of achieving a world first: 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 the failures, inactive molecules and undesirable outcomes.

**b) Reporting.**

Transparency in the reporting means that all onlookers knows what everyone 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 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 democratic platform where seasoned pharmaceutical professionals are able to interact with junior students. That the debate takes place at the same time as the research *allows the research to change direction before it is completed*.

**d) Design**

The technical platform uses existing online infrastructure3,4 allowing the widest number of people to participate, and builds/promotes open standards wherever it can. Improvements required in the future are actively promoted as part of the discussion so that others from outlying disciplines (*e.g.,* software development) can contribute.

**e) Publication**

OSM publishes its work in open access journals, but also makes use of other publicly accessible media to ensure full data availability for other researchers. Research papers are constructed in public, 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 shown openly, along with their biological efficacy, so it is clear to everyone which molecules are worth pursuing and which are not.

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 these students generating outputs that are useful in a real-world project, rather than generic laboratory outputs that are discarded.
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 know they will be impactful.
4. Avoidance of unnecessary duplication can be achieved by ceasing to work on a project that is being undertaken by another organization behind closed doors, as happened with OSM’s Series 2. Work ceased when it became known another team elsewhere was looking at similar molecules. Now this other team has published, research by OSM on those molecules could recommence.
5. OSM is decentralized. The team expands and contracts as needs arise. 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 followed. In Series 1, a significant debate arose about a potential weakness of the molecules lurking behind an otherwise impressive performance at killing the parasite. The debate, started by a spontaneous contribution from a world expert in the field and subsequently recorded on YouTube, led to research effort on the series being scaled back significantly. This decision saved considerable resources that would have been expended had the research been behind closed doors. The peer review has also saved resources when it has been noted by an onlooker that a molecule currently being planned for laboratory, can instead be purchased.

**d) Design**

The technical and infrastructure needs of OSM are publicly debated. It would be 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 was discussed, planned and proposed in a published research paper that can now act as a proposal for funds.5

**e) Publication**

The paper describing Series 1 was published alongside a considerable volume of supporting data that included compressed versions of all laboratory notebooks that can be browsed, allowing individual experiments to be seen and reused. The current writing of a paper on Series 4 involves assigning tasks to contributors, allowing federated contributions from everyone and employing Github as a public fileshare system. 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 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, and then attempt, new ways of creating a scaled-up model that is able to compete with the traditional pharmaceutical industry.6 One of the possibilities, for example, 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 this increase in core funding comes a better marshaling of community resources through a pyramid of mentors and mentees, while retaining 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 licence, meaning everything it generates may be used by anyone else for any purpose, including to make 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 if that is the most efficient way to help patients.

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

Ironically a major demonstration of avoiding research waste would come if an open source series failed in development. Lessons could be learned by all onlookers about why the series failed, and how such failure could be avoided by other series of molecules 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 drug development programs that are “parked” and then archived, awaiting 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), 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 a challenge to quantify because it is highly granular – there are many small savings across many projects over long periods of time, all 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) An Open Source Pharma Roadmap, M. Balasegaram, P. Kolb, J. McKew, J. Menon, P. Olliaro, T. Sablinski, Z. Thomas, M. H. Todd, E. Torreele and J. Wilbanks, *PLoS Med.* **2017**, 14(4): e1002276. DOI: 10.1371/journal.pmed.1002276

**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