James Schuler, Will Mangione, Ram Samudrala, Werner Ceusters
ICBO 2019 response to reviewer 1

---------- REVIEW 1 ----------
SUBMISSION: 29
TITLE: Foundations for a Realism-based Drug Repurposing Ontology
AUTHORS: James Schuler, William Mangione, Ram Samudrala and Werner Ceusters

---------- Overall evaluation ----------
SCORE: 2 (accept)
----- TEXT:
The manuscript presents the beginnings of an ontology to address the issue of drug repurposing. The authors survey the available terms that could be used for this purpose, evaluate their definitions, and propose improvements where needed.

Major concerns:
1) What is the purpose of Table 1 and the associated description? As is, it seems to just take space. The table, and the sentences between "Specifically, we used the general Google search engine..." and "The search parameters..." (inclusive) can be deleted with no loss of information needed by the reader.
This purpose of the table and associated description is to provide justification for our work, as it highlights the dearth of related work.

2) The term "scattered molecular aggregate" indeed seems incorrectly defined by the original authors (attributed to DrOn in this manuscript, but see point 3 of my "Minor issues"). Looking at the "inspiration" for the definition (as documented within the term annotation), it seems likely that the original definition should simply have been ended at "...part of a more massive material entity" (removing what comes after about other aggregates). That alone would remove the cause of the inconsistency noted by these authors. The redefinition of SMA to "an object aggregate that consists of all molecules that are located in some bounded region" lacks one important part--the scattering. By the new definition, a drug in pill form is also a scattered molecular aggregate. This seems unintuitive.
We claim a scattered molecular aggregate does not have to be a part of some “larger” entity. The SMA exists both in pill form and in distributed form throughout the body, whereas the drug product only exists in pill form. The SMA of ibuprofen molecules in a pill of Advil is the same SMA as when it is distributed throughout the body. Before ingestion, the SMA made of ibuprofen molecules was part of some drug product. Our definition for SMA allows us to speak of some portion of molecules as a powder, then as part of drug product, and then in the body (perhaps in a widely distributed form).

3) I see no reason to redefine "treatment" to achieve the authors' aims. The proposed definition would render two identical regimens (say, intended to cure strep throat) as either treatment or not, depending purely on the outcome. This again seems unintuitive. A better solution would be to add a child term, below treatment, called (for example) "successful treatment". That should be all that's needed. That being said, I agree with the authors that the current definition of treatment is not quite right. Rather than appealing to some hypothesis of a cure, treatment should be defined in terms of previous demonstrated success. Note that doing so does not require success in every application.

We understand that every clinician who does something with the intention to make the patient better, would like to call that something a treatment. We recognize that our proposed definition of treatment implies that not all such intended treatments would be classified as treatment. That is intentional: we believe entities should insofar possible never be defined on the basis of what is known or hypothesized about them. However, our definition of treatment does not necessitate total amelioration from a disease or the total disappearance thereof: what is required is some influence on the realization of a disease toward homeostasis. In the case of strep throat, i.e., a certain kind of infection in the pharynx, if a person ingests some portion of compound (perhaps in a drug product), and some members of the infectious agent group are destroyed, and the body is able to replace some portion of cells in the throat, but there are other causative organisms present, then there was a process which influenced the realization of a disease toward homeostasis, albeit not a curative one.

Consider a disease with a chronic disease course, e.g., essential hypertension or diabetes. Clearly, drugs can bring the body back to homeostasis – normal blood pressure and euglycemia, respectively – but the disease is still present.

Furthermore, in any given instance of a planned process with a hypothesis of success, even given all known evidence, it is not for certain what the outcome of such a planned process will be. A ‘treatment’ that doesn’t work is not a treatment under our definition.

4) The statement in paragraph 5 of Discussion/Treatment that "the disposition to treat a particular disease inheres in all instances of a scattered molecular aggregate" is not true. There are certainly scattered molecular aggregates that were never intended to treat anything. Please revise to indicate the intended point.

We agree that our wording is ambiguous, and we have revised the paragraph. Our intent was to highlight only the cases where the disposition actually inheres in the SMA. We certainly agree that not all SMAs have a disposition to treat a given disorder. With this statement we were emphasizing that the disposition of a specific SMA to treat a given disorder *always* inhered in that SMA, regardless of whether or not this was known to science. For example, if tomorrow we discover that aspirin can treat multiple myeloma, we would contend that the disposition of aspirin to treat multiple myeloma always existed (for as long as multiple myeloma existed in humans).

Minor issues:
1) In the introduction, the authors refer to the FDA as being part of the pipeline. Considering the international focus of the meeting, can they either state that the (latter parts of the) described pipeline refers to the USA? Or perhaps change FDA to "relevant government authority" or similar (assuming all else is the same everywhere, including the Phases I-IV clinical trials).
We will change this statement to reflect the international implications of our work.

2) Some of the sentences are rather difficult to read, owing either to twisty wording or to lack of punctuation.
- First sentence of paragraph 6 of the Introduction, that reads "Better than leaving drug repurposing being driven by coincidental observations...". This would be better as "In the above example drug repurposing was driven by coincidental observations. A better approach would be to turn it into an active search process."
- Same paragraph, the sentence beginning with "Although CANDO has already demonstrated to be successful..." should be revised for clarity:
"Although CANDO has already demonstrated success (3), our hypothesis is that a better ontological understanding of drug repurposing experiments--and of the relationship between drugs/compounds and diseases--will increase the benchmarking performance of the platform and the fidelity of our models to reality."
- First sentence of paragraph 4 of Methods/Literature review: Change "We did thus not..." to "We thus did not..."
- First sentence of the section entitled "Relevant existing ontologies": Change "In our work in attempting to define..." to "In our attempt to Define..."
Thank you. We have changed the text to your suggestions.

3) Several cases of mistaken provenance:
- "scattered molecular aggregate" is an OBI term, not DrOn.
- "treatment" is an OGMS term, not OBI.
We have fixed the provenance.

(By the way, kudos on the joke)
Thank you.

ICBO 2019 response to reviewer 2

---------- REVIEW 2 ----------
SUBMISSION: 29

TITLE: Foundations for a Realism-based Drug Repurposing Ontology
AUTHORS: James Schuler, William Mangione, Ram Samudrala and Werner Ceusters

---------- Overall evaluation ----------
SCORE: 1 (weak accept)
----- TEXT:
This manuscript reviews several ontological artifacts for possible reuse in drug discovery and drug repurposing software called CANDO/CANDOCK. They found several issues with these artifacts and propose corrections.

Some concerns:
1. They fault the Drug Ontology (DrOn) for the definition of 'scattered molecular aggregate' when DrOn MIREOTs this term from the Ontology of Biomedical Investigations for reuse. This fact does not invalidate their criticism of the definition, but it does impact the potential solutions to any issues raised. Changing the definition of SMA would be a request of the OBI developers and not the DrOn developers.
We realized our attribution mistake, and fixed the error. We believe the overall discussion is relevant and can gain contributions from OBI and DrOn.

2. Because the part of relation is reflexive (every material entity is part of itself), having only one SMA as a part is not inconsistent. However, DrOn uses the has_proper_part relation here, and so it is in fact, inconsistent. The axioms for drug product do imply that there is at least one other part besides one active ingredient.

So the text definition of 'drug product' is not problematic, but the axiomatic one is.

This reviewer agrees that a portion of powder all of one type of molecule (e.g. aspirin) could be a drug product. So perhaps the solution moves back to DrOn to use a reflexive part of relation instead of the irreflexive Has_proper_part.
Based on our work and your insights, we agree with a potential solution of using *part_of* instead of *proper_part_of* in the axiomatic definition.

3. The developers of DrOn have not, to the best of my knowledge, attempted to represent functions surrounding delivery of drug products. However, the language of the paper especially in the second column of the first page of the Discussion, seems to fault DrOn existing representations of functions, rather than calling this out as a lack of representation of certain functions. Indeed, the developers of DrOn have in previous publications, acknowledged this lack and identified it as future work (see Hogan et al. Therapeutic indications and other use- case-driven updates in the drug

ontology: anti-malarials, anti-hypertensives, opioid analgesics, and a large term request. J Biomed Semantics, 2017;8:10. DOI 10.1186/s13326-017-0121-5). So it's not a problem with existing representations of function, but a lack of representations of functions required by the authors use cases.

It is not a matter of attacking DrOn's lack of defining delivery of drug products, it is a matter of our solution fundamentally disagreeing about in what entity the therapeutic function/disposition inheres. DrOn contends the anti-disease function inheres in the drug product, whereas we would argue the function (and therefore disposition) inheres in the SMA within the drug product. To us, the drug product merely has a 'delivery' type function, since it is eventually destroyed.

4. If the authors, as they claim, are not proposing a general definition of the term 'discovery', then they should not—per the principles of ontological realism—have entry #1 in Table 2 called "Discovery". They should have a different term, perhaps "Documentary discovery". Or instead just stick to drug discovery and define 'drug discovery'.

We required ourselves to define 'discovery' so that we would then be able to define 'drug discovery' as a subtype. What we meant with 'not a general definition' for discovery, is that we do not include uses of the word 'discovery' as in a child discovering an Easter egg under some plan to hunt for Easter eggs.

5. The definition of 'treatment', which the authors attribute to OBI, is in fact the definition MIREOT'd by OBI from OGMS. Again, the authors make a source attribution mistake here.

We have fixed the attribution.

6. The authors make a convincing argument to move therapeutic functions to the SMAs bearing the active ingredient role. However, it remains true that an SMA of vancomycin that is part of a vancomycin oral tablet (SMA-#1) bears an instance of the function to treat pseudomembranous colitis, whereas the SMA of vancomycin in an IV formulation of vancomycin (SMA-#2) bears an instance of the function to treat bacterial endocarditis. Neither the tablet nor the portion of IV solution is a bearer of an instance of the other type of function. If one could somehow extract SMA-#1 from the tablet and formulate it for IV administration, then it would gain the function of treating pseudomembranous colitis.

We agree. However, we argue that the disposition to treat *either* of those conditions inheres in all instances of SMAs of vancomycin. The function only exists when the particular SMA is put in the correct drug product to enable the delivery to the proper location (manufactured for that purpose).

7. The powder under the tongue: we agree. Similarly, chewing aspirin-containing tree bark to relieve headache involves no drug product.

This is another good example which we now include in the manuscript.

8. The authors of DrOn, OBI, and OGMS are most likely to make changes if the authors log the issues they identified. Do the authors plan to do so? Have they already?
This work is the first step in a larger discussion we wish to have with authors of DrOn, OBI and OGMS. We have not formally logged issues we have identified. We are happy to work with everyone to reach the best solution.

James Schuler, Will Mangione, Ram Samudrala, Werner Ceusters
ICBO 2019 response to reviewer 3

---------- REVIEW 3 ----------
SUBMISSION: 29
TITLE: Foundations for a Realism-based Drug Repurposing Ontology
AUTHORS: James Schuler, William Mangione, Ram Samudrala and Werner Ceusters

---------- Overall evaluation ----------
SCORE: 2 (accept)
----- TEXT:
This manuscript presents preliminary work on representing entities relevant to the drug repurposing domain. The need for this work is clearly demonstrated, and the project described here constitutes some progress toward this useful goal. This work is acceptable for presentation at ICBO. The following suggestions should be addressed in the final submission.

The submitted PDF is apparently an image (not searchable, text not selectable). This should be fixed before final submission.
We apologize for this issue, but are unsure of how it happened. We will be sure to submit the expected form of a .pdf, and ensure with conference organizers the correct version is uploaded.

P1
The literature review is, in the abstract and elsewhere, described as "extensive". While the literature search seems fine, this exaggeration does not improve the paper.
We have removed the term "extensive" from the abstract.

"A typical process of drug discovery …." — is this the most typical kind of drug discovery process? It would be nice to give the reader a sense for approximately how many different kinds of drug discovery processes there Are.
A different example of a drug discovery process, high throughput screening, is now given.

P2

"[some data sources] include non-ontologic understandings of …"
This reader does not know what an ontologic or non-ontologic understanding is. Don't ontologies strive to capture scientific understanding of the phenomena they represent?
Yes, work in ontology strives to capture scientific understanding, however, we recognize that much of the work done by non-ontologists is not being described or captured in an ontological fashion. Previously, several of us have worked on CANDO, and the data sources we used are in a relational database format, described without any underpinning of ontology. This statement is our attempt to recognize our past work and a step toward total ontological understanding.

P3
Table 2 contains definitions and elucidations? Which are which?
We have removed the term "elucidations" from the Table 2 caption.

The definition for "drug discovery" would be better if it mentioned an organism.
'Homeostasis' from OGMS designates a disposition of the whole organism (or of some causally relatively isolated part of the organism, such as a single cell) to regulate its bodily processes in such a way as (1) to maintain bodily qualities within a certain range or profile and (2) to respond successfully to departures from this range caused by internal influences or environmental influences such as poisoning.
Therefore, the use of 'organism' in defining 'drug discovery' is redundant.

P4
"We do not claim to have proposed a general definition of 'discovery'…."
This is rather what it looks like from the label used. Why not collapse "discovery" and "drug discovery" into a single term if the sense of "discovery" aimed for applies narrowly to this work?
We required ourselves to define 'discovery' so that we would then be able to define 'drug discovery' as a subtype. What we meant with 'not a general definition' for discovery, is that we do not include uses of the word 'discovery' as in a child discovering an Easter egg under some plan to hunt for Easter eggs.

Throughout the "Discussion" section there is confusion over which terms are defined in which ontologies.
* DrOn does not define "scattered molecular aggregate" — OBI does.
* OBI does not define "treatment" — OGMS does
Including as footnotes or otherwise the URIs of the few specific terms that are critiqued here would aid the reader, and also aid the authors in determining which ontologies define the terms in question.
We have fixed the attributions. We are sorry for the error.
We have added footnotes of the term IRIs for: scattered molecular aggregate, drug product, and treatment.