The Oncologist, 2024, **XX**, 1–2
https://doi.org/10.1093/oncolo/oyae252
Advance access publication 24 September 2024
Editorial

Clinical trial results: each patient's participation should count

William D. Figg[1] and Susan E. Bates[2,3,*]

[1]Clinical Pharmacology Program, Center for Cancer Research, NCI, NIH, Bethesda, MD 20814, United States,
[2]Division of Hematology/Oncology, Department of Medicine, Columbia University Irving Medical Center, New York, NY 10032, United States,
[3]Hematology/Oncology Research, James J. Peters VA Medical Center, Bronx, NY 10468, United States

[*]Corresponding author: Susan E. Bates MD, Division of Hematology/Oncology, Department of Medicine, Columbia University Irving Medical Center, 161 Ft. Washington Ave., New York, NY 10032, United States (seb2227@cumc.columbia.edu).

The Oncologist's Clinical Trial Results (CTR) section was developed to be a templated, menu-driven report of a clinical trial that included the most salient facts about the study plus some discussion of the findings. This was developed as a response to a long-standing gap in publication that saw as many as half of clinical trials never published. Even among those that appeared as abstracts at the annual meeting of the American Society of Clinical Oncology, in 2016, 39% remained unpublished 4-6 years later.[1] The chief goal of the CTR section is to provide a venue where a valid clinical trial can be published, whether it had completed accrual or not, and even if it was deemed a "negative study." The trial must be IRB-approved, must have required informed consent, and must be listed on the NCI's clinicaltrials.gov registry. Most importantly, the CTR section is committed to the concept that patients enroll in clinical trials with the expectation that their participation will "count," that is, they will contribute to the knowledge base in oncology, and help others with cancer in the future. Most clinical cancer researchers have experience with trials being unpublished for one reason or another (eg, failure to fully accrue or a sponsor deciding to close a study). From our point of view, this has the potential for harm. Patients with cancer should not be exposed to a similar agent or combination that has already been shown to lack benefit or cause excessive toxicity.

This is the context in which the article "Homeopathic treatment as an add-on therapy may improve quality of life and prolong survival in patients with non-small cell lung cancer" by Michael Frass et al, was published in 2020.[2] As the editor of the CTR section when this manuscript was submitted, S.E.B. was puzzled by the positive survival benefit of the homeopathy mixture, an intervention that conventional wisdom has held confers benefit only by making patients feel better about their therapy. To make things more puzzling, the components of the homeopathic treatments were numerous and poorly defined. However, this trial enrolled 150 patients at 4 outpatient centers in Austria in a double-blind, 3-arm, multicenter study. The data included detailed information about the stage, quality of life, and symptom scales. The authors found that the homeopathic add-on therapy improved quality of life and overall survival. Soon after publication and onward, many readers objected to this paper, stating that it simply could not be true. A subset of *The Oncologist*'s editors have since taken time to re-review the work.

The key question is: Are there components in this homeopathic concoction that could be pharmacologically active? A large percentage of FDA-approved oncologic therapeutics are derived from natural products (eg, doxorubicin, paclitaxel, docetaxel, vinblastine, topotecan, teniposide, and etoposide, amongst others). That is why, for decades, the NCI had a team collecting every bark, root, sponge, and leaf from around the world for their drug screen program. Many of these compounds were so potent that they were too toxic for patients, even administered at very low doses, and development was discontinued for 2 decades or longer. Some (eg, maytansine, monomethyl auristatin E, and "deruxtecan") have been recalled from the dustbin as the payload on antibody-derived conjugates, which deliver toxic therapies directly to tumor cells, mitigating major systemic toxicity. The homeopathic concoction described in the article by Frass et al used a mixture of plant, mineral, and animal components in crude extracts, not fractioned pure compounds. Thirteen of the 37 plant ingredients included in the concoction do not specify the plant species, just the genus of the type of plant. If we examine the ingredients from the plants, 60% are considered toxic (poisonous ingredients in bold font; Table 1).

Pseudoscience tries to claim that one needs to ingest the whole plant or ground-up animal part to achieve the therapeutic benefit, but unfortunately, that is not science. Science says we should identify the chemicals from any plant/animal extract that might provide therapeutic benefit, discern the mechanism of action, and then understand its molecular pharmacology. This, of course, is not always easy. Nearly 50 years after first administering doxorubicin (Adriamycin), we still do not fully understand its mechanism of action. Table 2 lists some of the ingredients from Frass et al's homeopathy concoction that have been tested in the NCI drug screen.[2] The doubt many have about the article by Frass et al would be

Received: 23 August 2024; Accepted: 26 August 2024.

Table 1. Plants in the homeopathy preparation used in Frass et al.[2]

Plants	Poisonous?
Atropa belladonna **(deadly nightshade)**	**Yes**
Byronia alba	**Yes**
Chelidonium	**Yes**
Conium maculatum **(poison hemlock)**	**Yes**
Lycopodium (clubmoss)	No
Gelsemium	**Yes**
Strychnos ignatii	**Yes**
Strychnos nux vomica **(strychnine tree)**	**Yes**
Pulsatilla **(over 40 species)**	**Yes**
Rhus toxicodendron **(poison ivy)**	**Yes**
Staphisagria	**Yes**
Syzygium cumini (java plum)	No
Aconitum **(wolfsbane)**	**Yes**
Althaea officianalis (marsh mallow)	No
Astralagus membranaceus	No
Byronia cretica	**Yes**
Carduus marinaus (milk thistle)	No
Coccus	Some species
Citrullus colocynthis	No
Solanum dulcamara **(bittersweet nightshade)**	**Yes**
Echinacea	No
Eupatorium perfoliatum **(boneset)**	**Yes**
Guajacum	No
Hypericum (St. John's Wort)	No
Carapichea ipecacuanha	No
Kalmia	**Yes**
Lobelia inflata	Potentially
Daphne mezereum	Yes
Achillea millefolium (yarrow)	No
Okoubaka	Not likely
Ranunulus bulbosus (buttercup)	No
Secale	No
Symphytum	Conflicting information
Nicotiana tabacum **(tobacco)**	**Yes**
Thuja	No (yes in high doses)
Veratrum album	**Yes**
Colchicum	**Yes**

alleviated if science uncovered cytotoxic compound(s) in their homeopathy concoction, which in sufficient concentrations, had anticancer activity.

Table 2. Natural products in Frass et al's concoction that have been tested in the NCI 60 drug screen for anticancer activity.[3]

Atropa belladonna	No significant activity at 100 μg/mL
Conium maculatum	No significant activity at 100 μg/mL
Strychnos nux vomica	No significant activity at 100 μg/mL
Syzygium cumini	**Significant activity**
Althaea officianalis	No significant activity at 100 μg/mL
Astragalus membranaceous	No significant activity at 100 μg/mL
Bryonia cretica	No significant activity at 100 μg/mL
Citrullus colocynthis	**Significant activity**
Solanum dulcamara	No significant activity at 100 μg/mL
Eupatorium perfoliatum	No significant activity at 100 μg/mL
Hypericum perforatum	**Significant activity**
Achillea millefolium	No significant activity at 100 μg/mL
Nicotiana tabacum	No significant activity at 100 μg/mL

The Oncologist and its CTR section hope that—by turning to the laboratory to determine whether any fraction of a homeopathic remedy holds a thread of promise—science identifies what is in these mixtures and that, in turn, potential anticancer compounds are then developed through conventional pathways.

Conflict of Interest

The authors indicated no financial relationships. S.E.B., Editor-in-Chief of *The Oncologist*, was the editor of the Clinical Trial Results (CTR) section when the manuscript by Frass et al, was submitted and published. She recused herself from the initial re-review of the manuscript, which was instead conducted by multiple subject-matter experts.

References

1. Massey PR, Wang R, Prasad V, Bates SE, Fojo T. Assessing the eventual publication of clinical trial abstracts submitted to a large annual oncology meeting. *Oncologist*. 2016;21(3):261-268. https://doi.org/10.1634/theoncologist.2015-0516
2. Frass M, Lechleitner P, Gründling C, et al. Homeopathic treatment as an add-on therapy may improve quality of life and prolong survival in patients with non-small cell lung cancer: a prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter study. *Oncologist*. 2020;25(12):e1930-e1955. https://doi.org/10.1002/onco.13548
3. The NCI Program for Natural Product Discovery (NPNPD) Prefractionated Library. Accessed June 14, 2024. https://dtp.cancer.gov/organization/npb/npnpd_prefractionated_library.htm