

# Role of the Advanced Practice Provider in Clinical Trials: Contributions to the Management of Patients Receiving Inotuzumab Ozogamicin

MARY ALMA WELCH,<sup>1</sup> PA-C, JOANNE C. RYAN,<sup>2</sup> PhD, RN, and ILENE ANN GALINSKY,<sup>3</sup> BSN, MSN, ANP-C

From <sup>1</sup>MD Anderson Cancer Center, Houston, Texas; <sup>2</sup>Pfizer Inc, New York, New York; <sup>3</sup>Dana Farber Cancer Institute, Boston, Massachusetts

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Mary Alma Welch, PA-C, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030.

E-mail: mawelch@mdanderson.org

<https://doi.org/10.6004/jadpro.2017.8.6.6>

© 2017 Harborside Press®

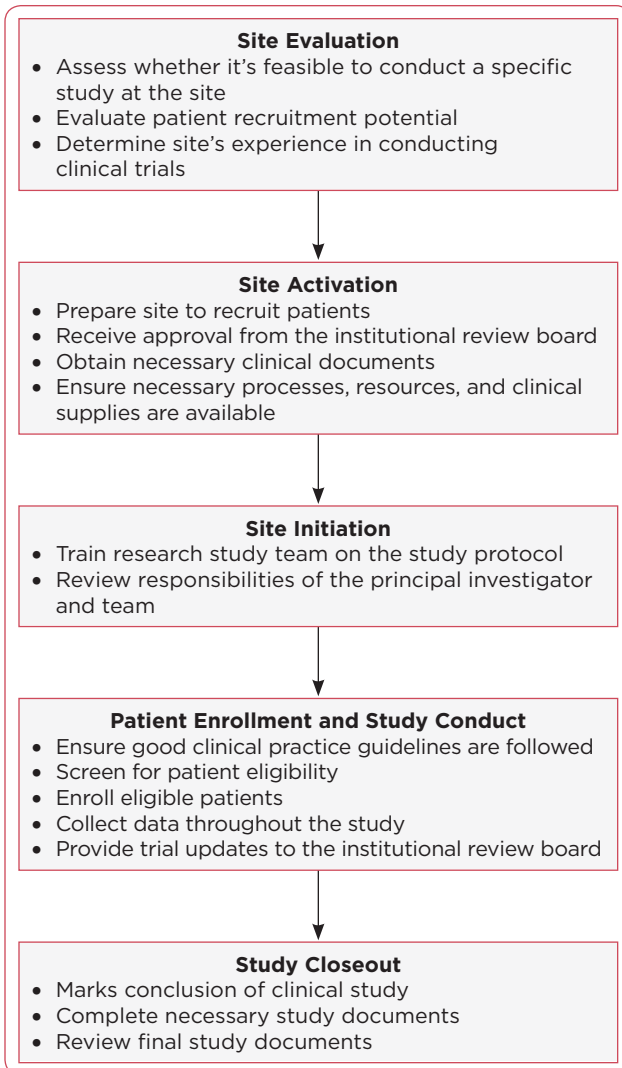
Successfully conducting oncology clinical trials requires the involvement of various research personnel. Advanced practice providers (APPs) are integral members of the team and play a vital role in identifying and enrolling appropriate patients, educating participants, and providing supportive care throughout the process.

Clinical research is crucial for developing new, more effective treatments and helping us to learn more about the efficacy and safety of existing therapies and novel combinations. Planning and conducting a clinical study involve several steps (Figure), and the various phases of clinical studies are designed to assess the appropriate dose, efficacy, and safety of new therapies (Table 1). In addition to advancing medical treatments and ensuring patient safety, maintaining data integrity is an important goal of clinical studies.

In this article, we highlight the role of the APP in clinical research through the experiences of a physician assistant and a nurse practitioner, both of whom have been active in the management of patients with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) treated with inotuzumab ozogamicin (InO) vs. the investigator's choice of chemotherapy in the phase III INO-VATE trial.

## UNDERSTANDING ACUTE LYMPHOBLASTIC LEUKEMIA AND INOTUZUMAB OZOGAMICIN

Acute lymphoblastic leukemia is a rare, life-threatening disease affecting lymphoid progenitor cells that occurs in adults and children (Curran & Stock, 2015; Pui, Robinson, & Look, 2008). Typically, adults have worse outcomes than pediatric patients (Curran & Stock, 2015), with complete remission (CR) rates roughly between 60% and 90% with current induction therapies (Bassan



**Figure.** Planning and conducting a clinical trial.

& Hoelzer, 2011; DeAngelo et al., 2015). However, some patients are refractory to initial treatment (Thomas et al., 2004), and as many as 60% of adult

patients relapse in the first 5 years after diagnosis (Kantarjian et al., 2004).

Standard treatment options for adult patients with R/R ALL are limited, and patient outcomes are poor (Oriol et al., 2010). The only potentially curative treatment following relapse is an allogeneic stem cell transplant. However, only a fraction of patients qualifies for this treatment, because in addition to finding an appropriate donor (Tavernier et al., 2007), eligible patients must have achieved CR (Gökbuget et al., 2012; Thomas et al., 1999). Therefore, there is an unmet need for additional clinical research and treatment options for adults with R/R ALL.

The role of APPs in caring for patients with ALL is particularly important given the patients' need for supportive care, frequent transfusion of blood products, and management of side effects. In our institutions, the APPs often see patients more frequently than the physicians.

In a large referral center with a dedicated leukemia department, education about disease biology and clinical course is a mainstay of the orientation process for APPs. Additional treatment-specific instruction occurs in several ways: interaction and collaboration with the principal investigator and research nurse, attendance at site-initiation visits and in-services provided by the study sponsors, attendance at national meetings and continuing education seminars, and day-to-day hands-on management of patients. A team approach is essential to appropriately monitor and report responses and side effects, so future patients benefit from the most up-to-date information.

The number of cancer therapies that target molecular factors necessary for cancer growth and progression is rapidly increasing (Ciavarella, Mila-

**Table 1. Phases of Clinical Trials**

Phase	Purpose	Number of participants
I	To test a treatment for the first time in humans to determine the appropriate dose and route of administration, identify side effects, and determine pharmacokinetics/pharmacodynamics	15-30
II	To determine the effectiveness of a treatment and further assess its safety	< 100
III	To compare the treatment with the current standard treatment, confirm its effectiveness, and monitor safety	100 to several thousand
IV	To gather additional information after a treatment is marketed regarding its effect in various populations and safety associated with its long-term use	Various

*Note.* Information from National Cancer Institute (2012); US National Library of Medicine (2008).

no, Dammacco, & Silvestris, 2010). Among them is inotuzumab ozogamicin, an antibody-drug conjugate comprising a humanized anti-CD22 monoclonal antibody conjugated to the cytotoxic antibiotic calicheamicin, which is currently being studied in patients with ALL (Shor, Gerber, & Sapra, 2015). Once bound by InO, CD22 (a cell-surface glycoprotein expressed on the surface of B cells of most patients [ $> 90\%$ ] with B-cell ALL; Boue & LeBien, 1988) is internalized into lysosomes, and calicheamicin is released to bind to the minor groove of DNA and induce double-strand cleavage with resultant apoptosis (Bouchard, Viskov, & Garcia-Echeverria, 2014; Shor et al., 2015). A phase II study in patients with R/R ALL showed InO was well tolerated and active, supporting further research in a phase III study (Kantarjian et al., 2013).

### ROLE OF ADVANCED PRACTICE PROVIDERS IN THE INO-VATE TRIAL

Advanced practice providers participated in all aspects of the phase III INO-VATE trial, an open-label, two-arm study (ClinicalTrials.gov identifier NCT01564784) evaluating the clinical activity and safety of InO compared with standard intensive chemotherapy (cytarabine, fludarabine, and granulocyte colony-stimulating factor, cytarabine plus mitoxantrone, or high-dose cytarabine; Kantarjian et al., 2016). Advanced practice providers functioned as subinvestigators and were registered with the US Food and Drug Administration, the sponsoring pharmaceutical company, and their institutions' research offices.

Once potential patients were identified in the clinic or hospital, the APPs worked closely with the attending physician and research team to recruit them and review their eligibility according to protocol guidelines. Typically, this process involved ensuring a patient fulfilled all of the clinical requirements of participation, such as adequate organ function, performance status, and ability to comply with study-required testing. Once eligibility was determined, the physician was responsible for obtaining consent, whereas the APPs played a major role in facilitating the consent process by educating the patients and answering patients' questions about how InO works, what monitoring tests are required, and what potential side effects to look for and how they can be managed. In this

role, APPs were on the front line in ensuring the well-being and safety of study participants.

In both of our institutions, patients are seen more frequently by APPs than by physicians for the routine review of labs and physical assessments and management of side effects. After a patient began treatment on the INO-VATE trial, APPs assumed a major role in direct patient care. Patients with ALL who receive therapy require frequent laboratory work and monitoring, sometimes as often as three to four times a week.

Common hematologic adverse events (AEs) observed with InO include thrombocytopenia, neutropenia, anemia, febrile neutropenia, and leukopenia; common nonhematologic AEs include nausea, pyrexia, diarrhea, and headache (Kantarjian et al., 2016). Advanced practice providers also monitored patients for important liver-related AEs, including increased aspartate aminotransferase and alanine aminotransferase levels, hyperbilirubinemia, and veno-occlusive disease. Advanced practice providers assessed AEs, including reviewing laboratory results and radiographic studies; determined the grading and causality of any AEs; and ordered concomitant medications or transfusions for appropriate management. Advanced practice providers also informed physicians of any AE patients experienced to aid with decisions regarding treatment delays, dose reductions, and treatment discontinuations.

In addition, APPs performed procedures such as bone marrow aspirates/biopsies, Ommaya taps, and lumbar punctures as clinically indicated for monitoring disease status and response to therapy. They also performed respiratory examinations, neurologic examinations, and complete physical examinations; administered intrathecal therapies; as well as prepared qualified patients for transplant. Among the most frequent interventions provided were intravenous fluid and electrolyte replacement; management of prophylactic antimicrobials; transfusion of packed red blood cells and platelets; and treatment of common complaints, such as nausea, vomiting, diarrhea, anorexia, and fatigue. Advanced practice providers also assessed the patient's need for growth factors and assessed when to coordinate central nervous system prophylaxis. The responsibilities of APPs in providing patient care and

monitoring not only apply to clinical trials, but also to the general care of any patient with a hematologic malignancy.

During clinical trials, APPs interact with, collaborate with, and educate other health-care professionals and clinical trial team members (Table 2). During the INO-VATE trial, APPs functioned as a resource for other clinical trial team members and for nurses caring for the pa-

tients. The APPs also served as liaisons between patients and the clinical study coordinator/research nurse to ensure assessments and other protocol-specific activities were conducted as required. Moreover, APPs played a vital role in facilitating a smooth transition to stem cell transplant in those patients who were eligible. They worked with the attending physician and pharmacist to determine the appropriate tim-

**Table 2. Key Roles and Responsibilities of Clinical Study Team Members<sup>a</sup>**

	<b>Roles and responsibilities</b>
APPs/ sub-investigator	<ul style="list-style-type: none"> <li>• Facilitate patient-consent process</li> <li>• Educate patients about research medication and adverse events</li> <li>• Assess and monitor adverse events</li> <li>• Provide direct patient care</li> </ul>
Principal investigator	<ul style="list-style-type: none"> <li>• Design and implement ethical research</li> <li>• Comply with all applicable federal regulations and ensure IRB submission and approval of all clinical research</li> <li>• Comply with and implement research according to IRB policies, procedures, decisions, conditions, and requirements; obtain prior IRB approval for changes</li> <li>• Obtain and document informed consent and assent</li> <li>• Report progress of approved research to the IRB</li> <li>• Report any injuries, adverse events, or other unanticipated problems involving risks to patients or others</li> <li>• Retain signed consent documents and IRB research records for <math>\geq 3</math> years past completion of the research activity</li> </ul>
Study physician/ sub-investigator	<ul style="list-style-type: none"> <li>• Manage patient care</li> <li>• Make decisions regarding dose delays, dose reductions, and treatment discontinuations</li> </ul>
Study coordinator	<ul style="list-style-type: none"> <li>• Collaborate with the principal investigator to ensure clinical trial is performed ethically and in accordance with regulations</li> <li>• Assist the principal investigator in preparing the study protocol as necessary</li> </ul>
Clinical research nurse and staff nurses	<ul style="list-style-type: none"> <li>• Deliver direct care to research participants and their families</li> <li>• Document all patient encounters in the medical record</li> <li>• Collect specimens as per protocol</li> <li>• Inform principal investigator/clinical trial nurse of patient- or protocol-related issues/concerns</li> <li>• Ensure protocol compliance</li> <li>• Collaborate with the research team to implement procedures for maintaining patient study participation from enrollment through completion</li> <li>• Ensure ongoing formal and informal communication regarding clinical trials with team members</li> <li>• Provide education related to clinical trials to patients and their significant others</li> <li>• In collaboration with the investigator, assess patients for adverse events and ensure symptom management</li> <li>• In collaboration with the investigator, evaluate disease response results and physical assessment data</li> <li>• Assist in patient-recruitment plans</li> </ul>
Clinical data manager	<ul style="list-style-type: none"> <li>• Abstract research data from patient's medical record/source documents to the case report form (paper or electronic) and enter data into database(s)</li> <li>• Conduct self-audits to ensure data quality</li> <li>• Provide periodic reports from database</li> <li>• Assist in preparation for audits/monitoring visits</li> </ul>

*Note.* APP = advanced practice provider; IRB = institutional review board.

<sup>a</sup>This table was adapted from the Roles & Responsibilities of the Research Team guidance (National Cancer Institute's Center for Cancer Research, n.d.) and developed based on the experience of the APPs authoring this article; roles and responsibilities of APPs in clinical research may vary depending on the institution and staffing, and there may be overlapping roles.

ing for the last dose of InO and coordinated the patient handoff from one team to another. Throughout the trial, it was important for APPs to communicate with the principal investigator and study coordinator/research nurse to ensure patients were managed per the study protocol and all necessary data were documented appropriately. Moreover, it was important for all clinical trial team members, including APPs, to work together as a team to ensure any changes to the study protocol were communicated to the appropriate parties.

The role of APPs in the INO-VATE trial serves as an example of the valuable part they play throughout the clinical research process. They are integral members of the clinical research team, working to ensure patient safety and the successful conduct of the trial.

**ROLE OF ADVANCED PRACTICE PROVIDERS AFTER THE INO-VATE TRIAL**

The responsibilities of APPs are not limited to patient care throughout the clinical research process but continue after the end of a clinical trial.

In the initially published efficacy results of the INO-VATE trial, which included 218 patients (Kantarjian et al., 2016), InO was associated with a significantly higher response rate than standard chemotherapy, both in remission and minimal residual disease negativity (Table 3). Minimal residual disease is defined as < 0.01% marrow blasts (Kantarjian et al., 2016) and is considered a surrogate marker for outcomes and survival (Knechtli et al., 1998; Lonial & Anderson, 2014). More patients in the InO arm proceeded to stem cell transplant than those who received standard chemotherapy (41% vs. 11%).

A total of 259 patients were included in the safety population. For patients receiving InO vs. standard chemotherapy, the incidence of grade ≥ 3 thrombocytopenia was lower (37% vs. 59%), there were fewer platelet transfusions (64% vs. 95%), and the incidence of liver toxicity and veno-occlusive disease was higher (11% vs. 1%; Kantarjian et al., 2016).

Understanding the efficacy and safety findings of the INO-VATE trial allows APPs to better educate and treat patients and to inform other health-care professionals about this promising therapeutic option. The experiences APPs gained from the INO-VATE trial also are invaluable for treating patients receiving InO through the compassionate-use program or investigator-initiated studies. Moreover, the knowledge APPs gained from the INO-VATE trial is useful beyond caring for patients administered InO and is also applicable to treating patients receiving other antibody-drug conjugate therapies.

**CONCLUSIONS**

Through their integral involvement in clinical trials, APPs contribute to advancements in therapeutic options. During the INO-VATE trial, APPs played a pivotal role by helping patients navigate consent forms; providing safe and innovative patient care, including managing infusion reactions, liver toxicity, myelosuppression, and other side effects associated with InO; and collaborating with other clinical trial team members. Through this experience, APPs learned about the importance of antibody-drug conjugate therapy, gained a wealth of experience, and positioned themselves to play an important role in educating their peers about the use of InO in the treatment of patients with ALL.

Inotuzumab ozogamicin was approved by the FDA on August 17, 2017, for the treatment of adults with relapsed or refractory B-cell precursor ALL.

**Table 3. Summary of INO-VATE Trial Efficacy Results**

	InO, n (%) [95% CI]	SC, n (%) [95% CI]	Rate difference, % [97.5% CI]	P value
CR/CRi	88 (80.7) [72.1–87.7]	32 (29.4) [21.0–38.8]	51.4 (38.4–64.3)	< .001
MRD negativity among responders				
CR/CRi	69/88 (78.4) [68.4–86.5]	9/32 (28.1) [13.7–46.7]	50.3 (29.9–70.6)	< .001

Note. CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; InO = inotuzumab ozogamicin; MRD = minimal residual disease; SC = standard of care. Information from Kantarjian et al. (2016).

The APPs who worked in the InO trial will now be able to bring their valuable experience to the nonclinical trial patients. ●

### Acknowledgments

The INO-VATE trial reviewed in this article is a clinical study sponsored by Pfizer Inc. Editorial support was provided by Anny Wu, PharmD, of Complete Healthcare Communications, LLC, and was funded by Pfizer Inc.

### Disclosure

Ms. Welch has no potential conflicts of interest to disclose. Editorial assistance was provided by Complete Healthcare Communications, LLC. Dr. Ryan is an employee of and has stock in Pfizer Inc. Ms. Galinsky has served on the advisory board for Pfizer Inc and has acted as a consultant for Novartis and Amgen.

### References

- Bassan, R., & Hoelzer, D. (2011). Modern therapy of acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *29*(5), 532–543. <https://doi.org/10.1200/JCO.2010.30.1382>
- Bouchard, H., Viskov, C., & Garcia-Echeverria, C. (2014). Antibody-drug conjugates—A new wave of cancer drugs. *Bioorganic and Medicinal Chemistry Letters*, *24*(23), 5357–5363. <https://doi.org/10.1016/j.bmcl.2014.10.021>
- Boue, D. R., & LeBien, T. W. (1988). Expression and structure of CD22 in acute leukemia. *Blood*, *71*(5), 1480–1486. <https://www.ncbi.nlm.nih.gov/pubmed/3258772>
- Ciavarella, S., Milano, A., Dammacco, F., & Silvestris, F. (2010). Targeted therapies in cancer. *BioDrugs*, *24*(2), 77–88. <https://doi.org/10.2165/11530830-000000000-00000>
- Curran, E., & Stock, W. (2015). How I treat acute lymphoblastic leukemia in older adolescents and young adults. *Blood*, *125*(24), 3702–3710. <https://doi.org/10.1182/blood-2014-11-551481>
- DeAngelo, D. J., Stevenson, K. E., Dahlberg, S. E., Silverman, L. B., Couban, S., Supko, J. G.,...Stone, R. M. (2015). Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia*, *29*(3), 526–534. <https://doi.org/10.1038/leu.2014.229>
- Gökbuget, N., Stanze, D., Beck, J., Diedrich, H., Horst, H. A., Huttmann, A.,...Hoelzer, D. (2012). Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*, *120*(10), 2032–2041. <https://doi.org/10.1182/blood-2011-12-399287>
- Kantarjian, H., Thomas, D., Jorgensen, J., Kebriaei, P., Jabbour, E., Rytting, M.,...O'Brien, S. (2013). Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer*, *119*(15), 2728–2736. <https://doi.org/10.1002/cncr.28136>
- Kantarjian, H., Thomas, D., O'Brien, S., Cortes, J., Giles, F., Jeha, S.,...Freireich, E. J. (2004). Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*, *101*(12), 2788–2801. <https://doi.org/10.1002/cncr.20668>
- Kantarjian, H. M., DeAngelo, D. J., Stelljes, M., Martinelli, G., Liedtke, M., Stock, W.,...Advani, A. S. (2016). Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *New England Journal of Medicine*, *375*(8), 740–753. <https://doi.org/10.1056/NEJMoal509277>
- Knechtli, C. J., Goulden, N. J., Hancock, J. P., Grandage, V. L., Harris, E. L., Garland, R. J.,...Oakhill, A. (1998). Minimal residual disease status before allogeneic bone marrow transplantation is an important determinant of successful outcome for children and adolescents with acute lymphoblastic leukemia. *Blood*, *92*(11), 4072–4079. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/9834212>
- Lonial, S., & Anderson, K. C. (2014). Association of response endpoints with survival outcomes in multiple myeloma. *Leukemia*, *28*(2), 258–268. <https://doi.org/10.1038/leu.2013.220>
- National Cancer Institute. (2012). Phases of clinical trials. Retrieved from <http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/phases>
- National Cancer Institute's Center for Cancer Research. (n.d.). Roles and responsibilities of the research team. Retrieved from [https://ccrod.cancer.gov/confluence/download/attachments/71041052/Roles\\_Research\\_Team.pdf](https://ccrod.cancer.gov/confluence/download/attachments/71041052/Roles_Research_Team.pdf)
- Oriol, A., Vives, S., Hernandez-Rivas, J. M., Tormo, M., Heras, I., Rivas, C.,...Programa Espanol de Tratamiento en Hematologia Group. (2010). Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica*, *95*(4), 589–596. <https://doi.org/10.3324/haematol.2009.014274>
- Pui, C. H., Robison, L. L., & Look, A. T. (2008). Acute lymphoblastic leukaemia. *Lancet*, *371*(9617), 1030–1043. [https://doi.org/10.1016/S0140-6736\(08\)60457-2](https://doi.org/10.1016/S0140-6736(08)60457-2)
- Shor, B., Gerber, H. P., & Sapra, P. (2015). Preclinical and clinical development of inotuzumab-ozogamicin in hematological malignancies. *Molecular Immunology*, *67*(2 Pt A), 107–116. <https://doi.org/10.1016/j.molimm.2014.09.014>
- Tavernier, E., Boiron, J. M., Huguet, F., Bradstock, K., Vey, N., Kovacovics, T.,...Thomas, X. (2007). Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia*, *21*(9), 1907–1914. <https://doi.org/10.1038/sj.leu.2404824>
- Thomas, D. A., Kantarjian, H., Smith, T. L., Koller, C., Cortes, J., O'Brien, S.,...Keating, M. J. (1999). Primary refractory and relapsed adult acute lymphoblastic leukemia: Characteristics, treatment results, and prognosis with salvage therapy. *Cancer*, *86*(7), 1216–1230. [https://doi.org/10.1002/\(SICI\)1097-0142\(19991001\)86:7<1216::AID-CNCR17>3.0.CO;2-O](https://doi.org/10.1002/(SICI)1097-0142(19991001)86:7<1216::AID-CNCR17>3.0.CO;2-O)
- Thomas, X., Boiron, J. M., Huguet, F., Dombret, H., Bradstock, K., Vey, N.,...Fiere, D. (2004). Outcome of treatment in adults with acute lymphoblastic leukemia: Analysis of the LALA-94 trial. *Journal of Clinical Oncology*, *22*(20), 4075–4086. <https://doi.org/10.1200/JCO.2004.10.050>
- US National Library of Medicine. (2008). What are clinical trial phases? Retrieved from <https://www.nlm.nih.gov/services/ctphases.html>