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GOG and CTEP Trials

The Gynecologic Oncology Group (GOG) has an almost 50-year history of generating practice changing trials in partnership with NCI/CTEP. Indeed, for almost every gynecologic cancer disease site the standard of care has been defined by GOG trials. The GOG is preparing a yearbook of its 50-year history that will be released in early 2014. Trials run through the GOG have led to two separate NCI clinical alerts and have led to remarkable improvement in survival in ovarian, corpus, and cervical cancers. Several factors have been keys to this high degree of success:

1. A longstanding and valuable partnership with CTEP;
2. The creation of a broad network of investigators – primarily gynecologic oncologists both in academic centers as well as community practices with a strong commitment to clinical trials and the GOG; and
3. A scientifically rigorous cooperative group membership with strong ties to NCI cancer centers, SPoRE programs, and the pharmaceutical industry

The GOG historically is much more similar to the Children's Oncology Group (COG) than the other adult Cooperative Groups in that it involves the majority of gynecologic oncologists in the country and is the single academic home for CTEP sponsored clinical trial development in a defined group of malignancies. Very similar to the COG, the GOG has been successful in improving outcomes in a wide range of rare tumors – predominately through the sustained commitment and identity that gynecologic oncologists and key medical oncologist and radiation oncologists have in the GOG resulting in a much higher enrollment on clinical trials than in other adult disease types. The GOG network consists of almost 200 separate gynecologic oncology practices throughout the country (representing a specialty of around 1000 board certified gynecologic oncologists). Historically, the GOG has been able to work with CTEP to take advantage of this strong physician identity within the GOG and to have unparalleled success in producing scientifically sound practice changing trials in gynecologic cancers. Crucial to this success has been the establishment and maintenance of the large national network of clinicians dedicated to the GOG as well key international collaborators.

An unintended consequence of the new restructuring of the Cooperative Groups with the creation of Disease Site Steering Committees (specifically the Gynecologic Cancer Steering Committee – GCSC) and the NCTN has been a rapid and sustained inability to open gynecologic cancer trials. This dramatic change threatens the continued existence of a viable network to carry out clinical trials in gynecologic malignancies. The purpose of this White Paper is to review the recent history of gynecologic cancer clinical trial development within the GOG (NRG Oncology), analyze the impact of the lack of trial development on the viability of the gynecologic cancer clinical trial network within this country, and to offer an agenda for action to salvage the gynecologic oncology clinical trials network. Failure to act

quickly and aggressively will lead to the dissolution of one of the most valuable and impactful components of the NCTN. Loss of the gynecologic oncology clinical trial network will disproportionately affect women and cannot be made up through other components of the NCTN (much as the loss of the COG would be devastating to the development of effective therapies in children).

Table 1: CTEP Sponsored GOG Trials

Year	Phase I	Phase II	Phase III	Total	Accrual Potential
2009	1	0	6	7	4198
2010	1	11	3	15	2689
2011	2	6	0	8	461
2012	0	6	3	9	1709
2013	0	1	0	0	**148**

Table 1 looks at CTEP sponsored trial activation for the GOG over the past six years. The ability of a cooperative group to survive is based upon activation of trials with enough accrual potential to allow individual investigators and groups to earn sufficient capitation dollars to support their research team of regulatory specialists, data managers, and research nurses. Historically, the GOG has averaged opening 10 to 12 trials annually with an annual accrual potential of around 3,000 patients. Table 1 shows a dramatic and sustained drop off of trial approval and accrual potential since 2010. The most recent year of 2013 has only one approved trial opening with an accrual potential of 148 patients. This **90% reduction** in available trials and accrual slots will have a devastating and potentially irreversible impact on the ability to do clinical trials in gynecologic malignancies in this country.

Table 2 looks at the seven year history of trial approval by the GCSC. Initially, the success ratio for trial approval was excellent and resulted in activation of several practice changing, innovative randomized phase II and phase III trials with enough accrual potential to sustain the group. In the past three years, however, there has been a drop off in approved trials.

Table 2: GCSC Action on Task Force Approved Trials by Year

	2007	2008	2009	2010	2011	2012	2013
Approve							
# trials	3	2	4	3	2	0	0
# patients	2008	1860	1554	890	597	0	0
Disapprove							

# trials	1	0	0	1	2	1	1
# patients	420	0	0	600	2800	60	2000

It is important to note that the trials brought to the GCSC have been based upon Clinical Trial Planning meetings and have been developed in conjunction with the appropriate disease site task forces which brought GOG, Spore, RO1 stakeholders, and other potential experts to the table. Each trial had received endorsement from the task forces prior to presentation to the GCSC. The discordance in endorsement by the task forces and approval by the GCSC points out a major problem in clinical trial development for gynecologic cancers.

The devastating impact of the past three years of lack of trial approval is illustrated below. Table 3 lists all CTEP endorsed GOG phase III trials currently open by disease site (as of 11-1-13). More impressive than the disappointingly few numbers of trials currently open is the fact that this will worsen considerably in the next six months. By the time the GOG integrates into NRG Oncology in March of 2014, the CTEP phase III trial accrual will be reduced to 201 patients annually. To put this in context, the annual accrual to phase III trials in 2010 and 2011 averaged 2190 patients. This 90% reduction in phase III trial accrual will eradicate the existing gynecologic oncology clinical trials network.

Table 3: Current (11-26-13) and Projected Accrual to CTEP Phase III Trials

GOG Trial	Population	Accrual	Target	Avg. Annual Accrual	Projection for 6 month
GOG 250	Leiomyosarcoma	107	130	30	Closed
GOG 258	Endometrial high risk	684	804	200	Closed
GOG 261	Uterine Carcinosarcoma – all	588	603	200	Closed
GOG 263	Cervix – RT post RH	143	534	55	55
GOG 274	Cervix - Outback	170	780	130	130
GOG 275	Gestational Trophoblastic disease – Act D/Mtx	10	381	9	9

GOG 277	Leiomyosarcoma – Obs vs. Chemo	4	216	7	7
Avg.				**631**	**201**

This loss of potential enrollment on phase III trials has not been offset by a concomitant increase in Phase II trials. As Table 4 demonstrates, the GOG is at best remaining static in phase II accrual. This includes extensive efforts at opening randomized phase II trials at the recommendation of CTEP and the GCSC.

Table 4: Current (11-26-13) and Projected Accrual to CTEP Phase II Trials

GOG Trial	**Population**	**Avg. Annual Accrual**	**Projected Annual Accrual in 6 months**
GOG 76	Cervix – Advanced	12	0
GOG 186	Ovary – Recurrent	240	120
GOG 229	Endometrium – Recurrent	90	90
GOG 238	Endometrium – Recurrent	17	17
GOG 264	Sex Cord Stromal Tumors of Ovary – BEP vs. C/T	10	10
GOG 265	Cervix – vaccine	8	8
GOG 279	Vulva – Chemo/RT	10	10
GOG 286B	Endometrium - Metformin	(Projected 200)	Estimate 100
Avg Annual Accrual		**387**	**355**

Because gynecologic malignancies are rare tumors, industry sponsors few trials in these diseases. Ovary has some potential historically, but due to the persistent FDA insistence on an overall survival advantage for drug registration in ovarian cancer there has been an astounding lack of interest by the pharmaceutical industry in running trials in the front line setting (which is historically where the GOG has had its most success in developing and running practice changing trials). There is modest interest in the recurrent disease setting and the GOG has worked with industry to diversify its portfolio in this area. There is very little interest by pharmaceutical companies to support trials in Uterine Corpus, Cervix, Vulva or any number of the very rare tumors we deal with. In anticipation of decreased support from CTEP the GOG has opened a GOG Partner's mechanism to work directly with the pharmaceutical industry. Table 5 catalogues the history of the GOG working to develop trials outside of the CTEP mechanism. As anticipated, the three open trials have all been in ovary. The upfront trial with Amgen was an international trial and will close after meeting half of its projected 2000 patient accrual due to an analysis which indicated it had a low likelihood of reaching a significant increase in OS (total US accrual to this trial was <300 patients).

Table 5: GOG Partner's Trials – Industry Sponsored

Partners Trial	**Population**	**Annual Accrual**	**Projected Annual Accrual in 6 months**
GOG 3001/AMG 386	Ovarian – Front Line	175	closed
GOG 3003/Vtx	Ovarian – Rec.	200	closed
GOG 3004/PARPi	Ovarian – Front line	150	50
Avg. Annual Accrual		375	0

The take home message from this analysis is that industry does not have enough interest in running a significantly diversified portfolio of gynecologic cancer trials to keep the GOG viable. Even when maximally engaged, industry is becoming increasingly wary of conducting ovarian trials in the US, is conducting more of these ovarian trials abroad, and is not interested in any meaningful trials in other gynecologic disease sites.

Due to the concern over the viability of the GOG, a leadership retreat was held on November 4, 2013 to better analyze the data presented above. Several consistent themes emerged:

1. The IOM Report stated a key goal of reorganization of the adult cooperative groups was to increase availability and access to clinical trials. The 90% reduction in accrual experienced by the GOG over the past few years clearly is in conflict with this goal.
2. The GOG is much more similar to the COG than other adult cooperative groups as comprehensive meaningful research in gynecologic malignancies within the US does not exist in the other cooperative groups.
3. There is a documented disconnect between the GCSC and the GOG/task force components of the NCTN. In addition, there is no clear consistent strategic guidance from CTEP or the GCSC leading to dissolution of the entire gynecologic oncology clinical trials system
4. The actions of the GCSC are difficult to interpret but are potentially being overly influenced by individuals from other countries who have a direct conflict of interest with a viable well-functioning clinical trials network for gynecologic malignancies in the US.
5. The inability of the GOG to participate in a meaningful way in the final deliberations of the GCSC has led to miscommunication and a high rate of trial disapproval. Of note, the exclusion of knowledgeable individuals from deliberations began around 2010 when CTEP became concerned with the high rate of approval of trials by the GCSC. This change has certainly had the intended effect of limiting trial approval as documented above.

A case illuminating the dysfunction currently pervading the system has been the failure to establish a phase III trial with PARPi (Veliparib) in ovarian cancer. The GOG completely restructured its protocol approval process to take into consideration the desire of CTEP to sponsor biology driven trials and anticipated the PARPi trial to be a model for developing research that meets all the areas that CTEP is now emphasizing. **Molecular pathway driven:** Ovarian cancer offers an outstanding venue for PARPi due to a 17% incidence of BRCA1/2 mutations as well as an additional 30-35% of patients who show defects in homologous recombination deficiency of DNA through other mechanisms. **NCI Sponsored Clinical Trial Meeting:** At a recent NCI sponsored Clinical Trials Planning Meeting focusing on molecular targets in ovarian cancer, the role of PARPi was selected as the most important biologic and clinical question in ovarian cancer. This outstanding translational symposium brought together SPoRE leaders, RO1 funded investigators, and the CTEP intramural program. **Building on GOG experience:** The GOG opened a sequence of phase I and II trials which have shown efficacy and tolerability of this compound both as a single agent (GOG-0280) as well as in combination with Carboplatin/Paclitaxel (GOG-9923). **Engaging OTF and CTEP in trial design:** Working closely with the Ovarian Task Force (OTF) as well as CTEP, multiple meetings for trial design were held with AbbVie as this represents a registration strategy for this company. The unique aspects of the trial are the fact that the PARPi will be given in the frontline setting in combination with standard cytotoxic agents as well as in the maintenance setting. **Translational research, biomarker analysis, cost effectiveness:** Three additional components were added to enhance the value of the trial: 1. an advanced imaging component in partnership looking at the role of perfusion CT as a biomarker in this population (building on exciting data generated in a previous GOG/ACRIN collaboration documenting the feasibility of this technique), 2. A cost effectiveness analysis (CEA), and 3. Molecular biomarker analysis for identifying homologous repair defects that have increased response to PARPi. **Submitting to GCSC after Ovarian Task Force Approval:** Extensive discussions were held with the OTF and the trial was submitted to the GCSC with strong endorsement.

Shockingly, the trial was disapproved. The GCSC and CTEP suggested two different randomized phase IIs as well as a number of other concerns. Since no one from the GOG was allowed to participate in the discussion of the trial during the GCSC conference call, potentially inaccurate information was accepted as fact. In an analysis of the point by point concerns listed by CTEP – all had been previously addressed with input from CTEP, the OTF, GOG, and the company but the GOG was not allowed to be present to discuss this fact. The main suggestion (a randomized phase II) was somewhat interesting in that the stated goal of the company when dealing with CTEP was a registry trial (in which case the FDA would not look favorably on a randomized phase II). To further complicate the matter, the GOG had previously turned down participation in a front line trial by a competitor (Olaparib) outside of the GOG due to our commitment to CTEP sponsored drug Veliparib. Since no gynecologic oncologists from the GOG were allowed to participate in the discussion, the GCSC filled this role with individuals from Europe (one of whom is a major supporter of Olaparib and has been the lead Principal Investigator in a number of studies with this compound). This astounding failure is just one example which highlights the complete disconnect between the US scientific community in gynecologic cancers (as represented by the GOG and Task Forces) and CTEP/GCSC. It also points to multiple areas of conflicts of interest and possible system manipulation which is devastating the gynecologic oncology trials network in this country.

We read with interest the **Interim recommendations made by the NCTN working group** that Disease Site Scientific Steering Committees should:

1. Increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN groups.
2. Optimize their use of Task Forces (TFs), Working Groups (WGs), and Clinical Trials Planning Meetings (CTPMs).
3. Emphasize biology-driven (e.g., molecularly-driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests and correlative science into study designs.

The virtual complete shutdown of the gynecologic oncology clinical trials portfolio is disturbing as the GOG has embraced working with Clinical Trials Planning Meetings, Task Forces, and Working Groups and has emphasized biology-driven trials and advanced surgical trials that incorporate biomarker tests and strong correlative science into study designs.

Recommendations of GOG leadership:

1. Meet with senior NCI/CTEP leadership to express genuine concern over the continued viability of performing gynecologic cancer trials in the US.
2. Meet with COG leadership to better determine their structure and working relationship with the Children's Oncology Steering Committee
3. Request an analysis of the GCSC and instances where there has been a disconnect with the GOG, Task Forces, Working Groups, and Clinical Trials Planning Meetings
4. Recommend that the GCSC either respect and accept the Task Force recommendations or eliminate the Task Forces as not being of value. The current process of working with the Task

Forces for months to years to get a trial ready for submission to the GCSC only to have all of them turned down is not only frustrating, it is an incredible waste of energy and resources.

5. If the GCSC and/or CTEP want to micro-manage the gynecologic cancer portfolio (and not work through the Task Forces, Working Groups, and Clinical Trials Planning Meetings) then there needs to be a mechanism in place for earlier and more fruitful engagement in the clinical trial development by these entities.
6. Limit potential for conflict of interest by not allowing international investigators on the GCSC to vote
7. Reduce the size of the GCSC considerably – it is currently composed of a large number of individuals who have very limited experience in gynecologic cancer clinical trials
8. Create a working relationship with the GOG so that more experienced US gynecologic oncology investigators can debate and vote on protocol approval. The challenge of having knowledgeable investigators on the call in other adult disease sites is not an issue. The Steering Committee may need to recuse a few individuals from voting because the trial is coming from a particular group – but the steering committee will still have seasoned, experienced US investigators who have participated in Task Forces, Working Groups, and Clinical Trials Planning Meetings on the conference call because there are members of other groups (i.e., SWOG, ECOG, or Alliance) who do not have to recuse themselves. When the GCSC discusses and votes on a trial almost everyone who has participated in these activities is not allowed to participate because they are senior members of the GOG. A good analogy for this broken process would be for the breast cancer disease group to have no US based trialists knowledgeable about breast cancer on the committee (to fill this gap with US gynecologic oncologists and breast oncologists from the international community alone), to make the committee very large, and to limit input and discussion from any breast researcher in the US who participates in Task Forces, Working Groups, Planning Meetings, or clinical trials. This is essentially what we are being asked to do. The data we have presented shows this process is not working.

We respectfully request that these issues be addressed in an expedient fashion to allow for the long term viability of gynecologic cancer research in the NCTN system as well as the US.

Appendix 1: NCTN WG Analysis of Gynecologic Portfolio

Strengths and Concerns of Gynecologic Portfolio

Strengths

- Recent increase in randomized phase 2 and phase 3 trials over single arm phase 2 trials
- Strong international collaborations
- Generally strong accrual record

Recommendations to Address NCTN WG Concerns

- Achieve better balance between innovative, science-driven trials and incremental/confirmatory trials
- Focus on translational science with clear endpoints and goals including greater collaboration with SPOREs and other translational investigators
- Pursue more systematic design of trials based on past positive or negative results
- For ovarian trials, include endpoints other that PFS and expand beyond the current focus on bevacizumab
- In the cervical portfolio, focus more on detection, prevention and radiation therapy trials
- GOG and GCSC along with the NCI should work together more closely in developing future strategic directions

SSC Process

Comments/Recommendations to Address NCTN WG Concerns

- Good progress in working with GOG and integrating GCSC, Task Force, and GOG processes for concept review
- Clinical Trial Planning Meetings (CTPMs) have been used effectively but could be improved by including more translational researchers and focusing future meetings on translational science
- Interact with the pediatric SSCs to share best practices on handling portfolios dominated by a single submitting group