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Formation of an international intergroup to coordinate clinical trials in head and neck cancers

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Title: Formation of an international intergroup to coordinate clinical trials in Head and Neck Cancers: HNCIG

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On behalf of all HNCIG investigators

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We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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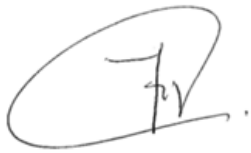
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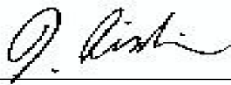
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Background

For decades, clinical trials have been the cornerstone of testing and establishing new therapies in cancers, including head and neck cancers (HNC). Academic research organizations conducting these trials face a constant struggle to accrue patients, both to advance treatment as quickly as possible and to minimize the substantial cost of these trials, which is strongly driven by their duration. Banding together institutions in national (e.g., the NCTN in the US, and NCRI in UK), international (e.g., EORTC in Europe), and global (e.g., GCIG, BIG, and SIOG for gynecological, breast, and pediatric cancers, respectively) consortia has been a successful strategy to expand patient catchment areas and increase accrual capacity for networks ¹. In some cases, particularly for rare cancers, this has enabled study of diseases that could not be studied by individual groups ^{2,3}.

A 2015 review of 694 HNC trials listed on clinicaltrials.gov showed a 13.1% early termination rate with insufficient accrual being cited as the most common cause for trial closure. A number of factors contribute to the difficulty of accruing patients to head and neck cancer trials: low global incidence of these cancers, different treatment approaches (surgical vs. non-surgical) across different institutions, high rate of comorbidities in this patient population, small number of experienced HNC physicians, poor performance status and treatment compliance due to the nature of the cancer, high treatment-related toxicity, and lack of patient awareness in clinical trials ⁴. In addition to these factors, a new barrier in HNC trial recruitment is the changing landscape of HNC tumor biology.

Previously, most mucosal squamous cell carcinoma of the head and neck (HNSCC) were attributed to tobacco and alcohol use; therefore, past trials included all HNSCC regardless of tumor locations or biology. Recent molecular and genomic advances have led to the global awareness that HNSCC is a heterogeneous entity that requires more precise clinical trial design for individual HNSCC subsets. For example, treatment de-escalation to decrease toxicity is now being tested in non-smokers with good prognosis human papillomavirus (HPV)-related oropharyngeal cancer (OPC) ⁵; whereas treatment escalation to improve outcome is being studied in smokers with poor prognosis HPV-negative OPC ⁶. Similarly, driver mutations are noted in small subsets of HNC ⁷, and trials are now designed to match targeted drugs with appropriate aberrant pathways. As clinical trials evolve to adapt to new knowledge in HNC biology, the overall pool of eligible patients for each trial becomes smaller, leading to more accrual challenges. Consequently, there is an urgent need for more international collaboration

to facilitate the conduct of clinical trials in rare HNC to bring new therapies to these tumors in a timely fashion.

The viability of academic clinical trials is limited not only by the difficulty of finding enough patients to satisfy trial sample size requirements, but the need to implement trials within a finite time frame spanning concept development to final analysis and dissemination of results. A study of 419 federally funded phase I-III studies performed in the US cooperative group system revealed that more than a third of these studies did not reach minimum projected accrual and that there was an inverse relationship between poor accrual and long clinical trial development⁸. Further, an analysis of historical data of phase III trials within this system indicated that failure to achieve threshold accrual rates early in the trial strongly predicted failure to ever successfully complete the trial⁹. Considering these findings, the US NCI established rules to automatically flag for closure any trial taking too long to develop¹⁰ or not reaching specified percentages of projected accrual at early time points¹¹. Phase III trials that fail to reach 20% of projected accrual at quarter 5/6 after activation will be administratively closed and those achieving between 20% and 50% of projected accrual at this point will be given six months to improve accrual. Other funders have similarly protected their investments by establishing policies that trigger recommendation for early closure based on a poor accrual trend; for example, the EORTC will consider closure of phase III trials when observed accrual during quarter 4/5 since first patient in is below 50% and/or when accrual during quarter 8/9 is below 80% of expected accrual (Vermoken, personnel communication).

While further international collaboration is a logical strategy to increase the accrual base, conducting trials between groups and across borders necessarily brings its own challenges including multiple review processes by funding bodies, sourcing and distribution of drug, alignment of protocol development and amendment processes, regulatory and ethics approvals across jurisdictions, and coordination of pharmacovigilance and data management^{12,13}. Given the emphasis on accelerating trial development from concept to first patient in, and on hitting projected accrual rates early in trials, creating ad hoc networks for individual trials is burdensome and risky.

Rather working *ab initio* on each trial, the HNCIG was established as a standing body to take on these challenges. After preliminary discussions by some people who started the ball rolling alongside the ASCO 2014 general meeting, twenty organizations from around the world involved in late phase clinical trials came together in Nice, February 2015, during ICHNO to establish the Head and Neck Cancer International Group (HNCIG) to coordinate the

development and contribute to the accrual of practice-changing trials in these cancers. Since then, the group has created statutes that define its mission, goals, organization structure, membership and initiated collaborative activities. Below are the summaries of the group's information, activities and aspirations.

HNCIG Mission and Goals

HNCIG is comprised of “international and national Cooperative Research Groups and Sites performing clinical trials and meta-analyses in head and neck tumors, which includes but is not restricted to those originating from the upper aero-digestive tract”. The overarching mission of HNCIG is “to promote and conduct high quality clinical trials and meta-analyses to improve outcomes for patients with head and neck tumor”. This will be achieved through international collaboration, a strong sense of common purpose, shared expertise, and mutual respect among the members. Therefore, the aims of the groups include the followings:

- Promote international collaboration
- Promote clinical and translational research
- Perform studies in rare tumors
- Stimulate evidence-based medicine
- Support educational activities
- Harmonize clinical trials and translational research guidelines

HNCIG Structures

Members can be any clinical research network or high-accruing single institution performing clinical trials and/or meta-analyses in the field of HNC. Members must have a track record of conducting, participating or reporting on Phase III trial(s) or large individual meta-analyses. The criteria for membership and continued participation are outlined in the statutes ¹⁴. In addition, statutes include provisions for non-voting partners representing industry, advocacy, or government regulatory authorities.

Figure 1 shows the structure of HNCIG. The board of directors is the decision-making body of the HNCIG and is comprised of one representative from each member. The board of directors vote on the executive officers (the chair, secretary and treasurer), who manage the day-to-day

affairs of the group. The statutes also define the role and function of several permanent committees shown in Figure 1.

HNCIG Activities and Aspirations

Since its formation, HNCIG has formalized the list of full members (Table 1), elected executive officers, as well as created the harmonization committee, whose role is to “advance international standardization related to head and neck cancer”. Within the harmonization committee are subcommittees focusing on consensus development of protocol endpoints, radiation therapy, surgical therapy and systemic therapy. The endpoint subcommittee is collaborating with the DATECAN Group ¹⁵ to harmonize the definition of each endpoint and to determine the best endpoints for HNC trials based on tumor stage and subsite. The radiotherapy subcommittee is generating guidelines for clinical target volumes of the primary tumor for the different head and neck mucosal tumor sites. In addition, a future goal of this subcommittee is to generate consensus of minimum core methodology and dataset for evaluation of radiotherapy quality and compliance and documentation of radiotherapy toxicity. Similar remits for establishing surgical consensus guidelines and principles have been set for the surgical subcommittee, which will be launched soon.

The HNCIG has also defined what constitutes a HNCIG trial: a late phase HNC clinical treatment trial that is open to international collaboration and involves two or more HNCIG member groups. Member organizations have been asked to review their current trial portfolios for trials that fit these parameters, and to consent to badging appropriate trials with a unique HNCIG identifier. Member groups have also been requested to reference the intergroup in publications resulting from these trials, either in publication titles or acknowledgments. These are listed as HNCIG trials on the website, hnc.intergroup.info ¹⁶. Going forward, member organizations have been asked to prospectively agree to such badging and publication considerations.

Going forward, the aspiration of HNCIG is to create a harmonized platform for members within the group to conduct clinical trials together in subgroups and rare forms of HNC to maximize patient accrual and shorten the trial timeline. In addition, the harmonized platform will facilitate across trial comparison as well as pooling trial data for meta-analysis. To achieve its mission, HNCIG will need to overcome certain logistic barriers that include regulatory directives that differ by countries and escalating financial challenges faced by funders such as the U.S. NCI, CRUK, and European Commission programs. Regardless, these barriers have been surmounted by the Gynecological Cancer Intergroup (GCIG), which has created a successful platform for

international trial collaboration in GYN malignancies. We believe that HNCIG, with its dedicated members, will be just as successful and will accelerate the introduction of much needed novel therapies to HNC patients.

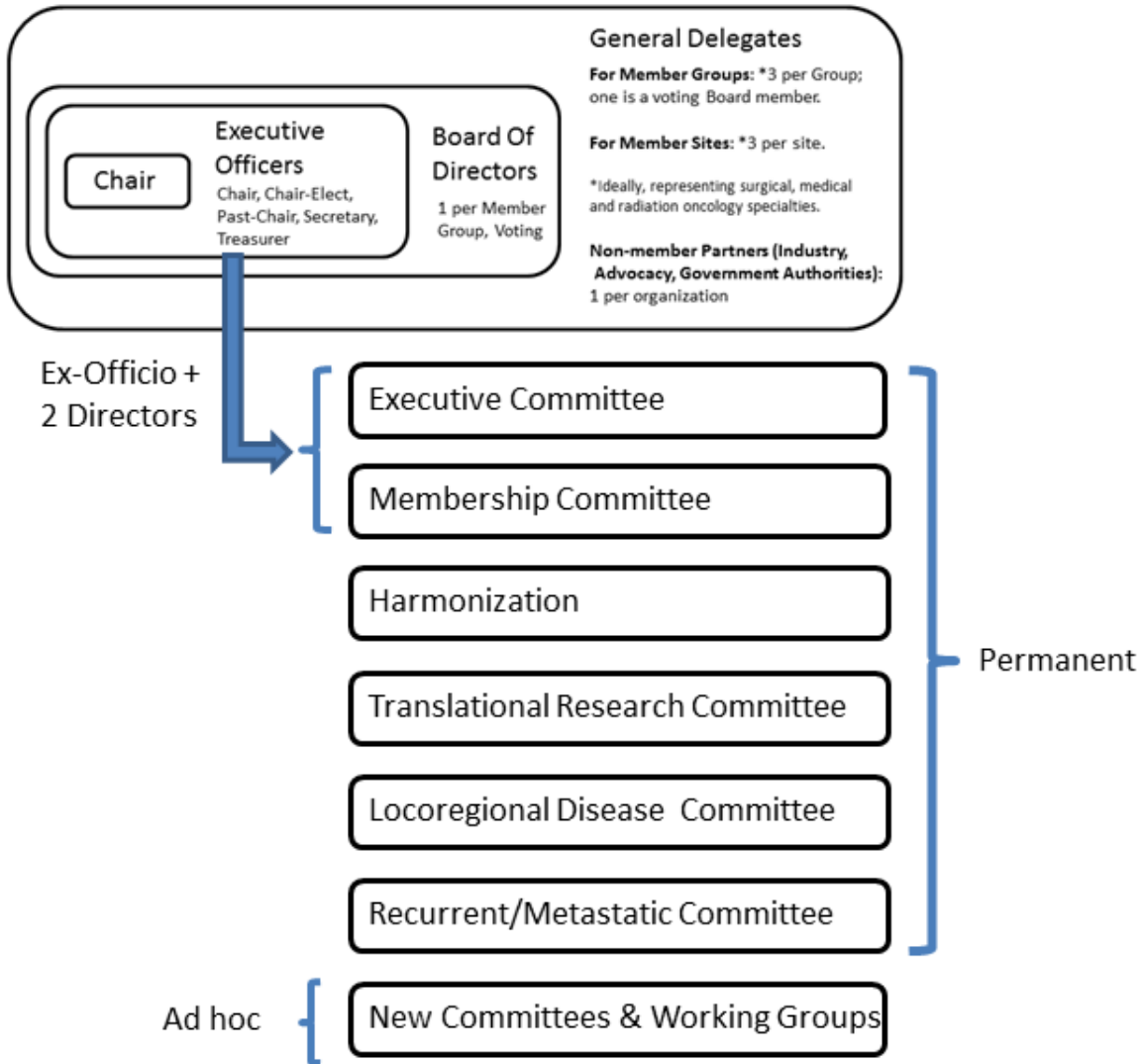


Figure 1: Organizational Chart for the Head and Neck Cancer Intergroup

Table 1. Members of HNCIG ¹⁷

Organization	Type	Main Accrual Base
Canadian Cancer Trials Group (CCTG, formerly NCIC-CTG)	Cooperative Group	Canada
Cancer Trials Ireland	Cooperative Group	Ireland
Danish Head and Neck Cancer Group (DAHANCA)	Cooperative Group	Denmark
ECOG-ACRIN	Cooperative Group	USA
European Organisation for the Research and Treatment of Cancer (EORTC)	Cooperative Group	European Union
Fudan University	High Accruing Center	China
Gruppo Oncologico del Nord Ovest (GONO)	Cooperative Group	Italy
Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC)	Cooperative Group	France
Hellenic Cooperative Oncology Group (HeCOG)	Cooperative Group	Greece
Hong Kong Nasopharyngeal Carcinoma Study Group	Cooperative Group	Hong Kong
Interdisziplinäre Arbeitsgruppe Kopf-Hals-Tumoren der Deutschen Krebsgesellschaft (IAG KHT)	Cooperative Group	Germany
Japanese Clinical Oncology Group (JCOG)	Cooperative Group	Japan
* MACH-NC Collaborative Group (Meta-Analyses of Chemotherapy in Head and Neck Cancer, Institut Gustav Roussy)	Meta-Analysis Group	Global
National Cancer Research Infrastructure, UK (NCRI)	Cooperative Group	UK
National Cancer Centre, Singapore	Cooperative Group	Singapore
Nederlandse Werkgroep Hoofd-Hals Tumoren (NWHHT)	Cooperative Group	Netherlands
NRG Oncology	Cooperative Group	USA
Tata Memorial Centre	High Accruing Center	India
Taiwan Cooperative Oncology Group (TCOG)	Cooperative Group	Taiwan
Trans-Tasman Radiation Oncology Group (TROG)	Cooperative Group	Oceania

** MACH-NC is a non-voting member of the HNCIG Board of Directors, as it does not conduct clinical trials.*

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