This supplement application focuses on increasing the sample size, rate of data collection, representativeness of the samples, and monitoring of studies proposed in U54 DA031659. The aims of the center remain unchanged. Project 1 includes two human studies evaluating the dose-response relationship for nicotine yield within the range thought to be at or below threshold for dependence and the potential use of concurrent nicotine replacement therapy (NRT) to facilitate the transition to VLNC cigarettes. This supplement will enable expansion of the first study in Project 1 from 3 sites recruiting 160 participants to 10 sites recruiting 840 participants in 1 year. We will also be able to assess additional experimental cigarettes directly related to the original aims of the proposal and conduct a small, within-subject test of the discriminability of different low nicotine content cigarettes. Project 2 is a multi-site trial assessing the effects of prolonged use of VLNC in a large sample and comparing immediately switching to VLNC cigarettes to gradually reducing the nicotine content in cigarettes over a period of 20 weeks. This supplement will enable expansion of Project 2 from 2 sites recruiting 500 participants to 9 sites recruiting 1250 participants in 2 years. Project 3 begins to address an important concern about the viability of a new standard for nicotine content in sub-populations (here we focus on smokers with schizophrenia) who might be particularly vulnerable to the effects of reduction in nicotine. The supplement will allow for faster data collection and improved data monitoring. Project 4 addresses concerns that the manipulation of other constituents in tobacco could offset the predicted gains of VLNC cigarettes by determining the relationship between the threshold dose for maintaining rat nicotine self-administration and the presence of minor alkaloids, betacarbolines, acetaldehyde, and MAO inhibitors. The supplement will enable additional experimental parameters to be included that will allow for better integration with the clinical projects. To accomplish these goals, we have established an Administrative Core (Core A), a Biomarkers Core (Core B), and a Biostatistics Core (Core C). Greater administrative oversight, quality assurance/study monitoring, methods for ensuring data integrity, and additional processing of biosamples are also requested as part of support from the cores.