Meinert C (2019). The trials and tribulations of the University Group Diabetes Program: lessons and reflections.

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Summary

The University Group Diabetes Program (UGDP) was an investigator-initiated secondary prevention trial funded by grants from the National Institute of Arthritis & Metabolic Diseases. Its purpose was to assess whether any of the commonly used agents for people with type-2 diabetes were useful in preventing morbidity associated with the condition.

The trial started in 1960 (first patient enrolled February 1961) and ended in 1981 (last follow-up examination done August 1975). The first publication of results came in 1970 and was prompted by a decision to stop using tolbutamide (Orinase®) in the trial because of evidence of ill-effects. In all, the study produced eight major publications (UGDP 1970d, 1970e, 1971a, 1971b, 1975, 1976, 1978, 1982).

Before the smoke settled, there were Congressional hearings, audits, court cases, and a request under the Freedom of Information Act for raw data from the trial which eventually wound its way to the U.S. Supreme Court.

As prevention trials go, the UGDP was relatively small – only 1,027 patients about evenly divided across five treatment groups – but what it lacked in size it made up by being in the forefront of secondary prevention trials. In the end, the principal trouble with the trial was that it produced results the world did not want to hear. When that happens the assumption is that there is something wrong with you and your trial because, surely, the world cannot be wrong.

The controversy surrounding the UGDP has been covered by Harry Marks, initially in his doctoral thesis, subsequently in his book *The progress of experiment: Science and therapeutic reform in the United States, 1900-1990* (Marks 1997). Details of the study and the controversy are featured in Chapters 7 and 49, respectively, of the 1st and 2nd editions of my textbooks (Meinert and Tonascia 1986; Meinert 2012), in chapter 5 of Aaron Mauck's PhD dissertation (2010), in chapter 4 of Jeremy Greene's book, *Prescribing by Numbers* (2009) and in a paper by Blackburn and Jacobs (2016). See also trialsmeinertsway.com for a detailed accounting of the trials and tribulations of the UGDP and for UGDP memorabilia.

This essay is from the perspective of an investigator in the coordinating center (deputy director) of the trial.

The UGDP

The project that was to become the University Group Diabetes Program (UGDP) was born of a question to Max Miller (UGDP study chair) by a Congressman in the late 1950s. The Congressman's daughter had just been diagnosed with type-2 diabetes and placed on Orinase® (tolbutamide) for control of her blood sugar. The Congressman wanted to know if blood sugar control was beneficial in reducing the complications of diabetes. Miller's answer was that no one knows because there have not been any trials to address the question. The answer came as a shock to the Congressman. The question galvanized a small cadre of people to set about organizing the UGDP.

The UGDP was an investigator-initiated multicenter randomized trial funded by the National Institutes of Health (NIH). It started with five clinical centers and ultimately grew to twelve. The coordinating center was located at the University of Minnesota in Minneapolis when the trial started and later at the University of Maryland.

The aims of the trial were:

1. Evaluation of the efficacy of hypoglycemic treatments in the prevention of vascular complications in a long-term, prospective, cooperative clinical trial;
2. Study of the natural history of vascular disease in maturity onset, non-insulin dependent diabetes; and
3. Development of methods applicable to cooperative clinical trials (UGDP 1970d).

The name of the trial has only four words and just 33 characters and hence is reasonably compact as names for trials go. *University Group* communicates something about where the study is done (though not all sites were university-affiliated) and that it is multicenter. *Diabetes* communicates focus, and *Program* denotes an activity that is planned to achieve a specified end. The acronym *UGDP* was largely immune from mischief, except by critics who referred to the study as the GD UP.

The downside of the name is that it is like the name of a child where you are left guessing if it refers to a boy or girl. *Program* as a currency word is nondescript. The preferred word is *Trial* but that word, at least when the study was formed, was viewed as anxiety-inducing for patients and was avoided.

The study treatments

When the UGDP started, people with diabetes were characterized as having "juvenile diabetes" or "adult-onset diabetes"; juvenile because of early onset and usually insulin-dependent; adult-onset because of onset in the 20s and beyond and usually not insulin-dependent. Those terms in the late 1970s gave way to type-1 and type-2 diabetes.

In 1960 the predominant treatment for type-2 diabetics was tolbutamide, marketed as Orinase® by the Upjohn Company of Kalamazoo, Michigan. The evidence was that the drug was effective in controlling blood sugar and, therefore, assumed to be beneficial long-term in reducing morbidity and mortality, but without any long-term trials to test this assumption.

UGDP investigators wanted to test tolbutamide long-term to see whether control of blood sugar conferred benefits in reducing morbidity and mortality associated with the condition. They wanted to do the testing against a placebo administered in a double masked fashion, where neither patients nor study personnel knew whether

persons were receiving tolbutamide or a matching placebo. They also wanted to test the efficacy of insulin long-term. The insulin treatments were not masked.

The treatments specified in the original study design were as listed below. The treatments were in addition to antidiabetic diets prescribed for all study patients.

Tolbutamide	Tolb	3 tablets/day; 0.5 gms tolbutamide/tablet; two tablets before breakfast and one tablet before evening meal
Placebo	Plbot	3 lactose placebo tablets/day on same schedule as Tolb
Insulin standard	IStd	U-80 Lente Iletin insulin; 10, 12, 14, or 16 units/day depending on person's body surface
Insulin variable	IVar	U-80 Lente Iletin insulin; as much insulin as required to maintain "normal" blood glucose levels (minimum dose 5 units/day)

Randomizations were stratified by clinic, arranged in permuted blocks of 16, ensuring that after every sixteenth enrollment there were exactly the same number of persons assigned to each of the four treatment groups in each clinic.

After the start of enrollment, phenformin (DBI-TD), came on the market (marketed originally by USV Pharmaceutical Corporation and subsequently by Ciba Geigy). As is often the case with new drugs, they are regarded as better and safer than existing drugs. Such was the case with phenformin in 1960. The hype caused some in the UGDP to argue for the drug to be added to the trial. Proponents of the drug argued that failure to include it would render the UGDP irrelevant, assuming phenformin lived up to its promise.

Investigators could not have known, when making their arguments in 1962, that they would stop using phenformin because of ill-effects before the trial was finished and that the drug would ultimately have the "distinction" of being the first and only drug removed from the market by the "imminent hazard provisions" power vested in the Secretary of Health, Education, and Welfare, because of deaths from lactic acidosis.

In 1962 the only question was how to add phenformin.

One option was to design a separate trial involving just phenformin and a matching placebo, creating, in effect, two trials – one with the original four treatment regimens and another involving just two treatment groups.

The other option was to add new clinics to the existing structure and modify the randomization design to allow assignment to phenformin and its matching placebo. This was the option ultimately chosen.

The treatment added are as listed below.

Phenformin	Phen	DBI-TD; 1st week: one capsule/day (50mg) before breakfast; thereafter one capsule before breakfast and 2nd capsule before evening meal
Placebo	Plbop	Matching placebo capsules; same schedule as for Phen

Anybody who has done a placebo-controlled trial knows that obtaining matching placebo tablets is almost impossible. Invariably, when compared side by side, the drug and placebo pills will have different sheens and subtle color differences. Indeed, one of the reasons why pills are often crushed and placed in capsules is because of the difficulty of matching appearances and shapes. If pills have company logos on them, it is illegal to produce placebos with those markings. Fortunately, in the case of the UGDP, tolbutamide tablets and matching placebo were provided by Upjohn with an almost perfect match. Phenformin and matching capsules were provided by the manufacturer. Insulin was provided by Eli Lilly.

Study sites, enrollment, and randomization design

The study involved five clinical centers when the trial started. Two more were added in 1961, three more in 1962, and two more in 1963, for a total of 12 clinical centers. The coordinating center was located in the School of Public Health at the University of Minnesota. It was relocated to Baltimore in 1963. The table below gives enrollment by treatment group by clinic. Note that only phenformin placebo was administered in five of the clinics and that six of the seven original clinics administered tolbutamide placebos only. One of the original seven clinics, the Boston clinic, was switched from the original randomization scheme after enrollment of the 32nd person to the scheme involving administration of phenformin and its corresponding placebo.

	Plbot	Tolb	IStd	IVar	Plbop	Phen	Total
Baltimore	24	21	21	20	0	0	86
Boston	8	16	16	15	8	23	86
Cincinnati	23	22	24	21	0	0	90
Minneapolis	22	24	24	24	0	0	94
New York	22	21	21	22	0	0	86
Cleveland	19	19	20	20	0	0	78
Williamson	23	23	24	24	0	0	94
Birmingham	0	12	12	12	12	38	86
Chicago	0	11	12	11	11	35	80
St Louis	0	11	12	11	10	35	79
San Juan	0	13	13	13	12	40	91
Seattle	0	11	11	11	11	33	77
Total	**141**	**204**	**210**	**204**	**64**	**204**	**1,027**

The randomization scheme as described below is taken verbatim from Gilbert et al 1975.

> *The UGDP study was arranged as a balanced design, stratified by blocks of 16 or 14 successive patients with-in clinics but without other restrictions on the pattern of assignment of treatment to subjects. Initially, during 1961 in each of seven clinics, the four treatments – variable-dose insulin (IVAR), standard-dose insulin (ISTD), tolbutamide, and placebo were allocated randomly to patients in blocks of 16–four subjects to each of the four treatments in random order. In 1962-1963, phenformin was added to the treatments at five new clinics as well as at one of the original seven and, in order to achieve overall parity in the total number of patients assigned to each treatment, the block size was*

fixed at 14, with each block containing six subjects receiving phenformin, and two receiving each of the four other treatments.

For purposes of administrative efficiency, individual patients receiving tolbutamide or placebo were not assigned uniquely identified medication but were supplied as follows: For the tolbutamide assignments, numbers 1 to 24 were split at random into two groups of 12, one group of numbers being assigned to placebo and the remainder to bottles that would be used for tolbutamide. Each of the first 24 subjects receiving placebo or tolbutamide in a given clinic was allotted a separate bottle number, the sequence then being repeated. Bottles 25 through 48 were used for patients assigned to tolbutamide in the clinics that also used phenformin.

As a consequence of this arrangement for the distribution of medication, sometimes two and at most three subjects in a given clinic were supplied with identical bottle numbers. The administrative advantage of this scheme is that each clinic could be given an initial supply of 48 uniquely labeled medications and could order additional supplies, as need arose, without burdening the central pharmacy with responsibility for more than 800 separately labeled medications.

The orally given medications in the tolbutamide study were in tablet form. The introduction of phenformin in the second part of the study required a change in the method of administration, since phenformin is supplied as granule-filled capsules. In this part of the study all control medication for new patients was given as capsules. Tolbutamide was still supplied as tablets but, unknown to the participating clinics, placebo in the form of tablets was not given in the phenformin clinics. New bottle numbers (49 to 72) were used for the capsules, but the same method of resupply was employed.

In executing this plan, lists of ordered treatment assignments were prepared in advance for each clinic by the Coordinating Center. Random permutations of 16 from the tables given by Cochran and Cox were used for the treatment allocations in the first six clinics, and the Rand tables were employed for those clinics in which phenformin was administered. The assignments were entered in a log book, and space was left on each list for entry of the name and identifying number of the patient and the date of assignment. To facilitate initiation of treatment, assignment requests could be made by the clinic to the Coordinating Center and filled by telephone, in which case a limited number of individuals had authority to record the name of the patient on the appropriate line of the log book, and report back the preselected therapy as shown on the list, that is, either ISTD or IVAR or a bottle number. Confirmatory letters were exchanged subsequently. Alternatively, the assignment requests might come by mail, and the response be reported in like manner. All treatment assignments were made in the sequence laid out in the randomization list.

Once treatments were assigned, therapy was initiated by the clinic. Insulin therapies, not being "blind," required no further consideration. In the case of orally given medication, however, the treatment was identified only by a bottle number.

Data collection schedule

The data collection schedule consisted of a qualifying baseline visit including a three-hour glucose tolerance test (GTT). To be eligible, patients had to have a sum blood GTT (fasting, 1-, 2-, and 3- hour values) of ≥500 mg/100 ml. The second visit one month later was when randomization took place. After randomization, patients were

counted as enrolled even if they never returned for follow-up visits. All patients were maintained on antidiabetic diets during the enrollment period, and thereafter, if enrolled.

After enrollment, patients were seen every three months. Each visit involved a general physical examination and an organ-specific examination; eye examination in quarter 1, heart examination in quarter 2, kidney examination in quarter 3, and peripheral vascular and neurological examination in quarter 4 and a sum glucose tolerance test. The sequence was repeated for each subsequent year of follow-up.

Results

The summary conclusions, as contained in study publications, are reproduced below. The tolbutamide and phenformin treatments were stopped because of ill-effects. The two insulin treatments made it to the end of the trial.

Tolbutamide result (UGDP 1970e)

> *All UGDP investigators are agreed that the findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or diet and insulin at least insofar as cardiovascular mortality is concerned. For this reason, use of tolbutamide has been discontinued in the UGDP.*

Phenformin result (UGDP 1971b)

> *This study provided no evidence that phenformin was more efficacious than diet alone or than diet and insulin in prolonging life for the patients studied. In fact, the observed mortality from all causes and from cardiovascular causes for patients in the phenformin treatment group was higher than that observed in any of the other treatment groups. In addition, there was no evidence that phenformin was more effective than any of the other treatments in preventing the occurrence of nonfatal vascular complications associated with diabetes. For these reasons, the use of phenformin has been terminated in the UGDP.*

Insulin results (UGDP 1982)

> *Mortality rates among the treatment groups were comparable. The differences in the occurrence of nonfatal vascular complications among the patients in these three treatment groups were small and only one of the drug-placebo differences was considered significant by the study criterion, and that was the insulin-standard versus placebo comparison for the occurrence of elevated serum creatinine levels (8.3% versus 18.5%, p value = 0.005). The occurrence of serious microvascular complications was surprisingly low. The latter finding as well as the slow progression of macrovascular complications underscores the differences in the course and the nature of the two principal types of diabetes mellitus, the rather stable and non-ketosis-prone maturity-onset type (type II) and the relatively unstable insulin-dependent juvenile-onset type (type I).*

Summary

1959	First investigators meeting
1960	NIH funding initiated

1961	First patient enrolled
1961	Two clinics added
1962	Phenformin treatment added
1962	Three clinics added
1963	Two clinics added
1966	NIH funding renewed
1966	Patient enrollment finished
1969	Tolbutamide treatment stopped
1970	Tolbutamide results published
1971	Phenformin treatment stopped
1971	Phenformin preliminary results published
1975	Phenformin final results published
1975	Patient follow-up ended
1981	NIH funding ended
1982	Insulin treatment results published

* * * * *

FDA audit

The FDA telegraphed its intention to revise the label for sulfonylurea drugs warning about cardiovascular risks associated with use soon after the tolbutamide results were published. The proposed relabeling riled the diabetic community because it was seen as heavy handed and precipitous in view of reservations regarding the validity of the UGDP results (Bradley et al 1975).

Since the labeling focused on a cause of death critics raised questions as to the accuracy of cause of death classification. The process of classification is detailed in the initial publication of the UGDP (UGDP 1970d).

Eventually, the FDA succumbed to pressures to audit UGDP death reports. The audit took place in the summer of 1977. The entire audit report is available on trialsmeinertsway.com/UGDPmemorabilia.htm.

The objective of the audit was to compare causes of death submitted by the participating clinical centers to the UGDP Coordinating Center with the causes of death assigned by the UGDP mortality review team and those published by the UGDP. It was not the intention of auditors to make a judgment on the cause of death but rather to determine if there were obvious discrepancies or errors in listing the cause of death. The auditors' conclusion was:

> *There appeared to be no such major discrepancies between the information available on these deaths and the cause of death assigned by the UGDP review team, although it is recognized that assignment of cause of death is a judgment and differences of opinion could arise when the information is reviewed by different individuals.*

Court battles (see Appendix for chronology)

The fun began with publication of the tolbutamide results in a supplement to *Diabetes* in November 1970. Unbeknownst to us investigators, the supplement also included a statement about the results from the AMA

Council on Drugs; a statement by Charles C Edwards, Commissioner of the Food and Drug Administration; and an editorial by Henry Ricketts, associate editor of *Diabetes*, reading in part:

> *The mortality study is at least suggestive enough to put a damper on what appears to be the indiscriminate use of all oral hypoglycemic agents in the treatment of mild or moderate, adult- onset diabetes. Although tolbutamide, for practical reasons, has been the only sulfonylurea drug investigated by UGDP, the chance that other compounds of this family may be similarly involved cannot be dismissed despite differences in molecular structure.*

The statements, all favorable to the UGDP, make it look to critics that we had orchestrated them. The Committee on the Care of the Diabetic (CCD) was formed the same month results were published, as a counterforce to efforts to relabel or withdraw tolbutamide from the market. The members of the CCD coordinating committee were (Bradley et al. 1975): Robert F Bradley, MD (chair) (Medical Director, Joslin Clinic, Boston); Henry Dolger, MD (Professor of Clinical Medicine, Mount Sinai School of Medicine, City University of New York, New York); Peter H Forsham, MD (Chief of Endocrinology, Professor, Department of Medicine, University of California Medical Center, San Francisco); Holbrooke S Seltzer, MD (Chief of Endocrinology, Professor of Internal Medicine, Veterans Administration Hospital, University of Texas Southwestern Medical School, Dallas); and Neil L Chayet, Esq. (15 Court Square, Boston).

Initially efforts of the CCD centered on blocking label changes for tolbutamide proposed by the FDA. The committee's efforts then expanded to blocking removal of phenformin from the market and to obtaining access to raw data from the trial.

The CCD regarded the UGDP as flawed and reasoned that if they were to gain access to its raw data they would be able to reanalyze and show where we went wrong. They wanted data forms that had been transmitted to the Coordinating Center from study clinics and computer tapes used in the Coordinating Center's analyses.

At about the same time, William Safire of the *New York Times* filed a request for Henry Kissinger's telephone notes from 21 January 1969 through 12 February 1971. That request was followed by another for all telephone notes while Kissinger was Secretary of State from both the Military Audit Project (28 December 1976) and the Reporters Committee for Freedom of the Press (13 January 1977).

Safire's request was denied on grounds that Kissinger was National Security Adviser during the time period covered in the request and that advisers to the President are not considered to be governmental agencies under the Freedom of Information Act (FOIA). However, the court of appeals did order the State Department to produce Kissinger's telephone notes for the other two requests.

The CCD's request and the two for Kissinger's telephone notes were heard at the same time by the Supreme Court (argued 31 October 1979 and decided 3 March 1980). The ruling in the Kissinger case was 4 to 2 against the requestors.

The ruling in the UGDP was 7 to 2 that

> *Written data generated, owned, and possessed by privately controlled organization as grantee of funds from HEW, held not accessible as 'agency records' under Freedom of Information Act when HEW never obtained data.*

The majority opinion in the UGDP was written by Justice Rehnquist and joined by Burger, Stewart, White, Blackmun, Powell, and Stevens. Brennan and Marshall dissented. [The opinion in its entirety is posted to trialsmeinertsway.com; tab "Historical Archive"].

The opinion in the UGDP hinged primarily on the fact that the NIH did not ask for data when the trial was ongoing. The ruling might well have been different if the trial had been done under contract with the NIH and subjected to closer monitoring by the agency.

Lessons

Publish first, present late

UGDP investigators, early on, agreed to a "publish first, present later" policy for primary results from the trial. However, as often happens, there is backsliding when faced with reality. The first test of the policy came with the decision to stop the tolbutamide treatment. The investigators ultimately decided in favor of presentation with the expectation of having the results published by the time they were presented. Big mistake!

Abstracts for three presentations (UGDP 1970a, 1970b, 1970c) were submitted for the 1970 American Diabetes Association meeting early in 1970. The pair of papers ultimately comprising a separate supplemental issue of *Diabetes* were submitted about the same time to the journal. For a time it looked as if the strategy was working, but things fell apart in late spring when the manuscripts were returned for revision.

In the end, the paper was published in November, about five months after the presentation in St. Louis. The intervening time meant that UGDP investigators stood helpless until the papers were published. The time gap was problematic. Diabetologists were deluged by calls from patients worried about the drug they were using. The fact that clinicians had to answer patients' questions without the benefit of a published report made them hostile to the study. By the time the publication finally appeared, they had long since decided that the study was "no good" and that there was no point in reading the published results.

Lesson: Publish first, present later!

Trust, but verify

Patients had to have a summary blood glucose tolerance test of ≥500 mg/100 ml to be eligible for enrollment (UGDP 1970d). The test consisted of a fasting value, and values at one, two, and three-hour post-glucose challenge. Glucose determinations were done at the clinic level. There had been discussions about sending specimens to a central laboratory, but that approach was rejected because of logistics and cost. The issue to be settled was whether determinations should be done using blood or serum. After a fair amount of discussion, the issue was decided in favor of blood.

Things proceeded uneventfully until, about three years after the start of enrollment, an investigator made an offhand remark during an investigators' meeting about the method used to determine glucose levels. Since the method cited was one requiring use of serum, another investigator questioned how the method could be used on whole blood.

> *"Whole blood? We use serum."*
>
> *"You do? The protocol specifies whole blood."*
>
> *"It does?"*

And so unfolded the “glucose story”, with the discovery that four of the twelve clinics were using serum instead of blood. When the smoke settled, the mistake was found to have affected entry determinations for 280 patients.

The mistake required the conversion of serum values to whole blood equivalents. Since serum glucose values are higher than whole blood values, the conversion resulted in 57 of the 280 patients having entry corrected summary GTTs below the diagnostic cut point of 500 mg/100 ml (UGDP 1970d).

***Lesson**:* It is not enough to specify requirements in a study protocol. One must also check adherence to the requirements.

On the meaning of ‘final’

Early on I labored producing forms for data collection. It was not my favorite activity, but I endured because I reasoned that it would be time-limited.

I was wrong!

Soon I learned that form changes and revisions of data collection forms are never ending. Often, before the ink was dry on one version there would be calls for revisions and additions. I smiled politely, playing deaf to the call; but I was ultimately outnumbered and overrun. The changes could range from correction of spelling errors to adding new sections to a form.

***Lesson**:* Delete the word “final” from your vocabulary when it comes to data collection forms and protocols in trials. Use version numbers on forms and key the numbers as data into the data system so the different versions can be identified and sorted at analysis time.

We can correct that

When a result is published and the world does not like it, people can always come up with some baseline variable that investigators failed to collect and attribute the result to imbalance in the variable, as was done with smoking history. Data were collected on current smoking habits but not on smoking history prior to enrollment. The Biometrics Committee characterized failure to include smoking history on enrollment as a blunder. (To my ear an unfortunate characterization because blunder means doing something stupid or careless.) The identification of smoking as a risk factor changed during the course of the UGDP. The foundation for data collection was laid in 1959, several years before the first report of the Surgeon General’s Advisory Committee on Smoking and Health (11 January 1964) and a year after that before warnings of health risks from smoking were required on cigarette packages.

In fact, the UGDP investigators did try to rectify the omission around 1972 with the collection of retrospective smoking histories. There were no major differences among the treatment groups attributable to smoking history. However, the results were never published because of questions involved in constructing baseline smoking histories long after patients had been enrolled and use of surrogate respondents for patients who had died.

***Lesson**:* Retrospective data collection is not the same as prospective data collection.

Seek and ye shall find?

Many of the lessons one learns in trials are “lessons” only because of shortsightedness. It should be apparent to anyone involved in long-term trials that one keeps track of everyone, even if they drop out, so that one can classify patients by whether they are alive or dead at the time of analysis. Anyone in charge of such efforts

knows that clinic personnel have to keep up-to-date "locator" information if there is to be any hope of tracing people. Even Inspector Clouseau knows that the chance of locating people lost to follow-up diminishes as a direct function of the time since last contact.

The protocol specified that clinics were to maintain "up-to-date" locator information for dropouts, but many clinics ignored that requirement. Hence, when it came time to produce the publication describing the tolbutamide mortality results, nine years after the start of enrollment, vital status was unknown in 23 dropouts in tolbutamide-assigned patients and in 24 placebo-assigned patients.

Clearly, a differential mortality rate among those people could be large enough to explain the observed tolbutamide-placebo mortality difference. Hence, it was obvious that investigators would have to delay publication in order to track dropouts to find out whether they were alive or dead.

Ultimately, through those efforts, investigators were able to assess the vital status of all but five patients: one person assigned to tolbutamide, two persons assigned to placebo, and another two assigned to the insulin-variable treatment group. The hard core unlocatables included a person named Wong, who moved to Chinatown in San Francisco, and was lost among 100s of other Wongs.

***Lesson**:* Keep the "locator information" current and make efforts to locate people lost to follow-up at yearly intervals to be ready for a decision to stop the trial – whenever it may come.

Who said you can vote?

The fateful day came in June 1969 when the Steering Committee was faced with an up or down vote on whether to stop use of tolbutamide. The voting policy (established early on) was two votes per center – two for each of the twelve clinics and two for the coordinating center (one vote for center directors and one vote for deputy directors) – but there was no clear policy on proxy votes, "stand in" voters in the absence of the director or deputy director, or even the designation of "deputy director." The ambiguities were noted when the policy was drafted, but considered unimportant because voting would be unnecessary in the expectation that major decisions would be by "consensus".

The first vote was close: 13 to stop tolbutamide and 12 to continue. After a show of hands there followed a debate as to who had voting rights, a sort of a precursor to the "hanging chad" problem at the 2000 presidential election in Florida.

***Lesson**:* The time to figure out who has a vote is before there are votes. Consensus is wonderful, but it is certain only in groups of size one.

What do you mean "The visit is missed?"

The patient visit schedule was in three-month intervals over the course of follow- up. Each visit consisted of a general examination and, depending on the quarter, an eye, heart, kidney, or peripheral vascular examination. Visits were numbered by quarter, i.e., FU 1 for the 3rd month after enrollment, FU 2 for the 6th month after enrollment, etc.

Well and good, except for what clinics did when patients missed a visit.

Suppose a patient does not show up for the 6-month visit, but does for the 9-month visit, i.e., the second follow-up visit for the patient, but the 3rd required visit according to the protocol. Does the clinic do the kidney exam or

the heart exam? Some clinics did the kidney exam and labeled the exam FU 3; others did the heart exam and labeled it FU 2. Needless to say, counting visits to produce performance statistics by clinic was impossible without hard and fast rules as to when a visit was counted as missed.

***Lesson**:* Construct contiguous time windows that specify the limits within which a visit is to be done. Visits not done in the specified time interval are missed; no "ifs", "ands", or "buts". Require clinics to file "missed visit" forms to enable the coordinating center to "count".

Mortality: The trump outcome

The trial was designed to assess the value of different forms of anti-hyperglycaemic treatments for prevention or amelioration of the late complications of type-2 diabetes. The sample size was derived by pragmatic considerations of money and numbers that could be reasonably recruited. There was only passing mention of mortality in the protocol because investigators did not believe that the trial would be adequately sized to find differences in mortality, if indeed the drugs produced benefit in reduced mortality. This, however, is not to say that mortality was not tracked or that investigators did not look for differences in mortality. Indeed, it is the mortality differential in the tolbutamide-assigned group in contrast to the placebo-assigned group that ultimately led investigators to stop use of tolbutamide and to publish mortality results.

Interestingly and surprisingly, critics suggested investigators had no basis for acting on the mortality differential, since mortality was not specified as an outcome of interest in the study protocol.

Lesson: Mortality is a "primary" outcome, whether or not used to produce a pre-trial estimate of the statistical power of the trial and whether or not specified in the study protocol. To ignore an important outcome, merely because it was not designated "primary", is to court danger for people enrolled in trials.

Stopping a treatment

The decision to stop tolbutamide raised a series of questions.

How do you unmask a treatment without unmasking other treatments?

Tolbutamide was administered double-masked. When tolbutamide was stopped, all patients receiving tolbutamide or the matching placebo were given new bottles of medication – all having the same bottle number (number 88) – to be taken on the same schedule as before. Investigators knew the bottles contained placebo but patients did not.

When should the tolbutamide treatment be stopped?

The options were to do it immediately by telephone or letter, or to wait until the next scheduled visits. The former approach was rejected as being unnecessary given the equivocal nature of the findings. Patients were told at their next regular clinic visit following the decision.

What should happen to patients after the stop?

Follow-up and regular examinations continued.

What should the cutoff date be for the publication dataset?

The date used was 7 October 1967. That date corresponded roughly to the time required for patients to cycle through their next scheduled follow-up visit after the stop decision and providing adequate time for data harvests by the coordinating center.

What were other patients told about the decision?
Nothing, but if patients asked, they were told of the decision.

Lesson: Stopping a treatment is more complicated than starting one (See Armitage 2013 for a thoughtful discussion on deciding when clinical trials should stop.)

Dealing with brickbats
The investigators plan was "mum's the word" about the tolbutamide results until they were published. But the plan fell apart when investigators decided to present the results at the American Diabetes Association meeting in June 1970 in anticipation of the results being published by then. They misjudged. The publication came months after the presentation.

The first report of results ran at 2:17 pm Wednesday 20 May 1970 on the Dow Jones ticker. It was a report from a Kidder Peabody analyst warning investor of results adverse to Upjohn. That the first report was on a financial service wire was no surprise in retrospect, given that sales of tolbutamide accounted for nearly half of all prescriptions for oral hypoglycemic agents at the time (Meinert and Tonascia 1986).

That report was followed in the next few days by articles in major newspapers, including the *Wall Street Journal*, *Washington Post*, and *New York Times* (Ledger 1970, Mintz 1970a, Schmeck 1970, Mintz 1970b) featuring headlines such as:

> *Safety of Upjohn's oral antidiabetic drug doubted in study: Firm disputes findings* (21 May 1970, Wall Street Journal)
>
> *Antidiabetes pill held causing early death* (22 May 1970, Washington Post)
>
> *Scientists wary of diabetic pill: FDA study indicates oral drug may be ineffective* (22 May 1970, New York Times)
>
> *Discovery of diabetes drug's perils stirs doubts over short-term tests* (8 June 1970, Washington Post)

By the time of the meeting it seemed that everyone knew of the results, including patients calling their doctors to find out if they were on that "killer diabetes drug".

The presentation in St Louis did nothing to quell the criticisms.

We were crucified in the throwaway medical journals and accused of grandstanding, data dredging, malfeasance, and fraud. We were to the *Medical Tribune* and *Hospital Tribune* what Jackie Kennedy Onassis at the time was to magazines at check-out counters in supermarkets – always on the front page. The Box below contains sample headlines.

Medical Tribune

> *Investigators question study group's findings* (Monday, June 29, 1970)
>
> *Experts challenge data, design of investigation* (Monday, July 6, 1970)
>
> *Irish study of antidiabetics contradicts findings in US* (Wednesday, December 15, 1971)

Why the conclusions of the UGDP are incorrect (Wednesday, June 4, 1975) *Biometric Report on UGDP study stirs skepticism* (Wednesday, June 11, 1975) *A UGDP "Miracle"?…Some UGDP questions* (Wednesday, August 27, 1975) *Doctors' debate. UGDP computer vs. clinical data* (Wednesday, June 23, 1976)

Hospital Tribune

2 Diabetes researchers quit over demand for "unanimity" (Monday, December 14, 1970)

Tolbutamide fiasco (Monday, December 14, 1970)

"Misleading impression" laid to UGDP report (Monday, February 22, 1971) *Danger is seen in hasty action on antidiabetics* (Monday, March 22, 1971) *Canadian diabetes group rejects UGDP study* (Monday, April 19, 1971)

3 Nonpartisan experts doubt worth of UGDP findings (Monday, July 25, 1971) *Why the conclusions of the UGDP are incorrect* (Monday, June 16, 1975) *Europe skeptical of Biometric Study of UGDP* (Monday, July 14, 1975)

The inclination was to respond to criticisms in the throwaway press, but it became clear that doing so would sap our energy, so we opted to sit on our hands. A more difficult question was what to do about criticisms published in peer reviewed journals. There were several over the years, starting with Schor 1971 and Feinstein 1971, then Seltzer 1972, again Feinstein 1976a, 1976b, Kilo et al 1980, and others. Most of these we answered. Responses are contained in UGDP 1972, Schwartz 1971, and Schwartz and Meinert 2004, and in Cornfield 1971 (see Cornfield 1976; Schlesselman 2015).

Lesson: Keep your head down. You still have the rest of the trial to run.

Data sharing

The UGDP was into data sharing before it became an expected requirement of trialists. The publication of the tolbutamide results in 1970 (UGDP 1970e) contained a listing of data relating to deaths reported in the publication. A data listing for all 1,027 persons enrolled in the study was available on request as per an announcement in the 1977 December issue of *Diabetes* (UGDP 1977). The final publication in 1982 (UGDP 1982) contained 30 pages of data listings for all patients enrolled in the UGDP as of the end of data collection, 31 August 1975. Paper listings and magnetic tapes of baseline and follow-up data for all study patients were deposited at the National Technical Information Service in 1983 (UGDP 1983a, 1983b).

Lesson: It is not evident that the listings did anything to satisfy critics of the trial.

After the fact consent to randomized treatments

Institutional Review Boards (IRBs) did not exist when the UGDP started. There were no consent forms for patients to read and sign. It was left to clinic personnel to decide what to tell patients why they were being approached for study.

In reality, the requirement for informed consent to research on people existed long before the start of the UGDP: it is the first item in a ten-point manifesto that emerged from the Nüremberg war crimes trials (known as the Nüremberg War Code) promulgated in 1947 (Shuster 1997).

> *The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have:*
>
> *sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.*

In an article entitled *The MRC randomized trial of streptomycin and its legacy: A view from the clinical front line* (Crofton 2006) reported that "Neither group of patients knew that they were in a trial, which remained confidential throughout its 15-month duration". (Medical Research Council 1948, 1944)

Though the requirement for consent existed well before the UGDP was planned, the requirement was largely ignored. The prevailing view in a then paternalistic medical profession was that discussions regarding such issues as randomization to select the treatments patients were to receive would be anxiety-inducing and, hence, to be avoided.

That changed in the mid-1960s with accounts of a few "celebrated" studies involving people in research without their consent. Among them, one involved infecting "mentally defective" children in the Willowbrook State Hospital in New York with hepatitis and another involved the injection of live cancer cells into patients in the Jewish Chronic Disease Hospital in New York City. A publication by Beecher in the *New England Journal of Medicine* in 1966 (Beecher 1966) focused attention on the issue of ethics in clinical research. The outrage led the Surgeon General of the U.S. Public Health Service to announce, 8 February 1966, that henceforth, in order to receive funding, NIH grantees would have to provide evidence of procedures and practices designed to ensure documented informed consent. The order and its implementation eventually led to the creation of institutional review boards.

The problem for UGDP investigators was that the order came about when enrollment was complete. Memory no longer serves as to what investigators did to comply with the order, but whatever they did there is no evidence of widespread departures from the study based on seeking consents.

Lesson: There is no immunity from changes in regulations. You just have to roll with the flow when they come.

The label changes

The tolbutamide-placebo difference in cardiovascular mortality was striking. The conventional p-value for the difference was 0.005 when tolbutamide was stopped. But even with that, it is likely the results would have faded into obscurity had it not been for the efforts of the FDA to relabel the drug warning of cardiovascular risks associated with its use.

The opening salvo from the FDA was telegraphed in a Bulletin issued from the FDA by the Commissioner, Charles Edwards, and included as front matter in the *Diabetes* supplement containing the tolbutamide results.

The proposed relabeling had medical-legal implications in that it opened the door to legal action if persons on the drug experienced heart attacks. The concern regarding relabeling was a driving force behind the creation of the Committee on the Care of the Diabetic (CCD).

Efforts of the CCD focused on forestalling the relabeling. The CCD began its efforts in a request to the Commissioner of the FDA (7 October 1971) to delay the relabeling. A delay was granted on 7 November 1972 (after the label had already been printed and supplied to manufacturers).

Thirteen years after relabeling had been proposed it was eventually accomplished. The warning is reproduced below.

> ***Special Warning on Increased Risk of Cardiovascular Mortality:*** *The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups* (Diabetes, 19 (Supp.2):747-830, 1970).
>
> *UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of tolbutamide and of alternative modes of therapy.*
>
> *Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.* (Physicians' Desk Reference (PDR); 39th edition; 1985; pg 2,130)

The relabeling was a Pyrrhic victory for proponents of the change. By the time it was incorporated in the label, the diabetes world had moved on to other drugs that were not in the sulfonylurea class.

Lesson: Do not practice medicine based on what it says in label inserts.

Reflections

The third aim of the UGDP was "development of methods applicable to cooperative clinical trials".

It was a given that someone in the trial had to monitor results for quality control and for treatment differences. It was clear that responsibility for monitoring fell to the coordinating center, but not who should see interim treatment results. Ultimately it was decided that the entire steering committee (comprised of the director and

deputy director of each of the 12 clinics and the director and deputy director of the coordinating center) should see them.

The practice of monitoring and reporting to the steering committee in relation to its semiannual meetings was well established when the mortality trend against the tolbutamide treatment group began to emerge. At first the trend was a matter of curiosity, but it came to be a focus of concern in 1968.

The fact that monitoring in the UGDP was done by the steering committee raised concerns of bias and conflicts of interest. Tom Chalmers, associate director of the NIH and Director of the NIH Clinical Center during the tolbutamide decision, was critical of the fact that investigators involved in the trial monitored results to decide if treatments should continue. He regarded investigator involvement as constituting a conflict of interest. (Chalmers, Amacher 1982)

The issue raised ultimately (1998) led the NIH to require monitoring bodies for all multicenter trials it funds.

> *It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB). (10 June 1998)*

That requirement has led to an increasing number of trials with watertight separation of monitoring bodies from study investigators because of concerns that investigators, having knowledge of data trends, may bias data collection.

The trend is an unfortunate legacy of the UGDP because isolation of monitors from study investigators reduces the competency of the monitors to the extent that investigators, who collect the data, know the protocol and quicksand traps in the data better than their external counterparts.

Even worse is the tendency to mask the monitors to treatment assignment, again because of desire to avoid bias that may creep in if monitors know treatment assignment. That practice is what led me to write, “Masked monitoring, blind stupidity?” (Meinert 1998).

John Hampton (2015) in his paper “Therapeutic fashion and publication bias: The case of anti-arrhythmic drugs in heart attack” notes:

> *Disturbances of heart rhythm (arrhythmias) are common during and soon after heart attacks (myocardial infarctions), and these arrhythmias often precede and lead to early death. In the 1970s, it was found that the local anaesthetic drug lignocaine (lidocaine) suppressed arrhythmias, and it seemed obvious that giving anti-arrhythmic drugs would reduce the risk of early death after heart attack. The problem was that this obvious theory was wrong, but this was difficult to recognise from small clinical trials looking only at effects on arrhythmias, not outcomes that really matter, like deaths.*

Similarly, for treatments used to control blood sugar in people with diabetics, it seems obvious that such control will confer benefit in reducing the risk of morbidity and mortality associated with the condition. Obvious – until the UGDP.

The reality is that most trials are too small and short-lived to produce results bearing on long-term safety and efficacy. The median sample size for NIH-funded phase 3 and 4 trials is only 306 for phase 3 trials and 108 for phase 4 trials (Gresham et al. 2018).

Testing diabetes drugs is akin to 'whac-a-mole' at fairs. As soon as you knock a mole down, another one pops up.

The profit producing life of patented drugs is largely synonymous with the period of patent protection afforded drugs, typically 20 years from when the patent was issued. The period of protected marketing may be half that after subtracting time needed to bring a drug to market.

After patent protection expires other manufacturers are free to market generic brands of the drug. This reality means that drug companies have to recover their development and marketing costs and make a profit before patents expire.

Tolbutamide (Orinase®) used in the UGDP has since been replaced by other members of the family of sulfonylurea compounds. The FDA label warning fashioned after the UGDP applies to all members of the family but there is no way of knowing if the same risks apply to other members of the family without additional trials.

The number of people in the U.S. living with diabetes has increased steadily since 1960 (https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). The majority are type-2 diabetics.

Year	**US pop with diabetes (millions)**	**% US pop with diabetes**
1960	1.59	0.91
1985	6.13	2.62
2000	12.05	4.40
2010	21.13	6.75

The CDC estimates that of the 21 million people with diabetes in the U.S. in 2010 being on treatment, over half were on oral drugs alone (14% on insulin alone). In 1990 there were 23.4 million such prescriptions and 91.8 million in 2001 (Wysowski et al. 2003). Glipizide and glyburide, sulfonylurea compounds, accounted for 77% of all prescriptions in 1990 and 33.5% in 2001.

Alexander and coworkers (Alexander et al 2008) in a 2008 publication on national trends in treatment of type-2 diabetes mellitus from 1994 through 2007, report a decrease in sulfonylurea use (decreased from 67% of

treatment visits in 1994 to 34% in 2007). By 2007, biguanides (54% of treatment visits) and glitazones (thiazolidinediones) (28%) were leading therapeutic classes.

Perhaps, an unsung contribution of the UGDP, because of the controversy it created, is what it did to stimulate the development of other long-term diabetes trials.

The Diabetes Complications Control Trial (DCCT), started in 1983 and published in 1993, involved 1,441 people, but is only of marginal relevance to the question addressed by the UGDP. DCCT investigators excluded type-2 diabetics and the trial involved only insulin treatments (tight control via insulin pumps or by three or more injections of insulin based on frequent blood monitoring versus conventional insulin treatment involving one or two insulin injections per day). The investigators concluded that:

> *Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM.* (Diabetes Control and Complications Trial Research Group 1993)

Of more relevance is the UK Prospective Diabetes Study (UKPDS). Started in 1977 and closed in 1997. It involved 3,867 people with type-2 diabetes. Patients were randomly assigned to a sulphonylurea (chlorpropamide, glibenclamide, glipizide), insulin, or diet. Investigators concluded that

> *Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes. None of the individual drugs had an adverse effect on cardiovascular outcomes. All intensive treatment increased the risk of hypoglycaemia.* (UK Prospective Diabetes Study Group 1998)

Last word

The UGDP, being my first exposure to trials, was an unparalleled learning and enriching experience. I am thankful to Chris Klimt for hiring me on for what was to become a life as a trialist. Thank you, Chris!

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Appendix

Chronology of Court battles, 1970-1984

1970	November	Committee on the Care of Diabetic (CCD) formed
1971	June	FDA outlines labeling changes for sulfonylureas (Food and Drug Admin, 1971)
1971	October 7	CCD petitions FDA commissioner to rescind proposed label change
1972	May	FDA reaffirms position on proposed labeling change (Food and Drug, Admin 1972)
1972	June 5	FDA commissioner denies CCD 7 October 1971 request to rescind proposed label change
1972	July 13	CCD requests evidentiary hearing before FDA commissioner on proposed labeling changes (Food and Drug Admin 1975)
1972	August 3	Commissioner of FDA denies 13 July 1972 CCD request for evidentiary hearing (US Court of Appeals 1973)
1972	August 11	CCD argues to have the FDA enjoined from implementing labeling change before the United States District Court for the District of Massachusetts (US Court of Appeals 1973)
1972	August 30	Request to have the FDA enjoined from making labeling change denied by Judge Campbell of the United States District Court for the District of Massachusetts (Food and Drug Admin 1975, US Court of Appeals 1973)
1972	October 17	Second motion for injunction against label change filed by CCD in the United States District Court for the District of Massachusetts (US Court of Appeals 1973)
1972	November 3	Temporary injunction order granted by Judge Murray of the United States District Court for the District of Massachusetts (US Court of Appeals 1973)

1972	November 7	Preliminary injunction against proposed label change granted by United States District Court for the District of Massachusetts (Food and Drug Admin 1975)
1973	July 31	Preliminary injunction vacated by Judge Coffin of the United States Court of Appeals for the First Circuit. Case sent back to FDA for further deliberations (Food and Drug Admin 1975, US Court of Appeals 1973)
1973	October	FDA hearing on labeling of oral agents (Food and Drug Admin 1975)
1974	February	FDA circulates proposed labeling revision (Food and Drug Admin 1975)
1974	March-April	FDA holds meeting on proposed label change, then postpones action on change until report of Biometrics Committee (Food and Drug Admin 1975)
1974	Sept 18-20	Testimony taken concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee (US Senate Select Comm 1974)
1975	January 31	Additional testimony concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee (US Senate Select Comm 1975)
1975	July 9, 10	Additional testimony concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee (US Senate Select Comm 1975)
1975	September 30	CCD files suit against David Mathews, Secretary of Health, Education, and Welfare, et al., for access to UGDP raw data under the Freedom of Information Act (FOIA) in the United States District Court for the District of Columbia (US District Court NY 1975)
1975	October 14	Ciba-Geigy files suit against David Mathews, Secretary of Health, Education, and Welfare, et al., for access to UGDP raw data under the FOIA in the United States District Court for the Southern District of New York (US District Court NY 1975)
1975	December	FDA announces intent to audit UGDP results
1976	February 5	

		United States District Court for the District of Columbia rules UGDP raw data not subject to FOIA (US District Court 1976)
1976	February 25	CCD files appeal of February 5 decision in United States Court of Appeals for the District of Columbia Circuit (US Supreme Court 1978)
1976	October	FDA Endocrinology and Metabolism Advisory Committee recommends removal of phenformin from market (Food and Drug Admin 1977a)
1977	March 8	United States District Court for the Southern District of New York rejects Ciba-Geigy request for UGDP raw data (US District Court NY 1977)
1977	April 22	Health Research Group (HRG) of Washington, DC, petitions Secretary of HEW to suspend phenformin from market under imminent hazard provision of law (Food and Drug Admin 1977a)
1977	May 6	FDA begins formal proceedings to remove phenformin from market (Food and Drug Admin 1977a)
1977	May 13	FDA holds public hearing on petition of HRG (Food and Drug Admin 1977a)
1977	July 25	Secretary of HEW announces decision to suspend New Drug Applications (NDAs) for phenformin in 90 days (Food and Drug Admin 1977b)
1977	August	CCD requests that United States District Court for the District of Columbia issue an injunction against HEW order to suspend NDAs for phenformin†
1977	September 20	FDA audit report (trialsmeinertsway.com/PDFs/UGDP/Doc_27 UGDP%20Audit%20September%2020%201977.pdf)
1977	October 21	CCD request to United States District Court for the District of Columbia for injunction against HEW order to suspend NDAs for phenformin denied†
1977	October 23	NDAs for phenformin suspended by Secretary of HEW under imminent hazard provision of law (Food and Drug Admin 1977c)
1978	January	Appeal of October 21, 1977 court ruling filed by the CCD in United States Court of Appeals for the District of Columbia Circuit
1978	July 11	Judges Leventhal and MacKinnon of the United States Court of Appeals for the District of Columbia Circuit rule that public does not have right to UGDP raw data under the FOIA. Judge Bazelon dissents (US Court of Appeals 1978, US Supreme Court 1978)
1978	July 25	CCD petitions United States Court of Appeals for the District of Columbia Circuit for rehearing on July 11 ruling (US Supreme Court 1978)
1978	October 17	Petition for rehearing at the United States Court of Appeals for the District of Columbia Circuit denied (US Supreme Court 1978)
1978	November 14	Results of FDA audit of UGDP announced (Food and Drug Admin 1978)
1978	November 15	FDA Commissioner orders phenformin withdrawn from market (US Supreme Court 1980)
1979	January 15	CCD petitions the United States Supreme Court for writ of certiorari to the United States Court of Appeals for the District of Columbia Circuit (US Supreme Court 1978)
1979	April 10	Appeal of October 21, 1977 ruling denied†
1979	May 14	Writ of certiorari granted

		UGDP case of Forsham et al., versus Harris et al., argued before the United States Supreme Court (US Supreme Court 1980)
1980	March 3	United States Supreme Court holds that HEW need not produce UGDP raw data; 7 to 2 decision (US Supreme Court 1980)
1984	March 16	Revised label for sulfonylurea class of drugs released (Food and Drug Admin, 1984a, 1984b, 1984c)

†Personal communications with Robert F Bradley, Joslin Diabetes Center, Boston (1st chair of the CCD).