

## Summary

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The UGDP was an investigator-initiated secondary prevention trial funded by grants from the National Institute of Arthritis & Metabolic Diseases. The purpose was to determine if any of the commonly used agents on type 2 diabetics were useful in preventing the morbidity associated with the condition.

The trial spanned 21 years. Funding started in 1960 and ended in 1981. The first patient was enrolled February 1961 and the last followup examination was done August 1975. The first publication of results came in 1970 in relation to a decision to stop the use of tolbutamide (Orinase®) in the trial because of ill-effects. All together the study produced eight major publications (UGDP 1970d, 1970e, 1971a, 1971b, 1975, 1976, 1978, 1982)<sup>62,63,58,60,55,54,52,51</sup>

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

The UGDP, as prevention trials go, 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 prevention trials. In the end, the principal trouble with the trial was that it produced results the world did not want to hear and 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 (1997)<sup>24</sup> in his book *The progress of experiment: Science and therapeutic reform in the United States, 1900-1990*. Details of the study and the controversy are also featured in Chapters 7 and 49, respectively, of the 1st and 2nd editions of my textbooks (Meinert, 1986; 2012)<sup>30,28</sup> and more recently in a paper by Blackburn and Jacobs (2016).<sup>2</sup> See also [trialsmeinertsway.com](http://trialsmeinertsway.com) for a detailed accounting of the trials and tribulations of the UGDP and for UGDP memorabilia.

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# The University Group Diabetes Program Story

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## 1. Introduction

- 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 followup ended
- 1981 NIH funding ended
- 1982 Insulin treatment results published

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 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 were:

1. Evaluation of the efficacy of hypoglycemic treatments in the prevention of vascular complications in a long-term, prospective, and 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).<sup>62</sup>

Naming a study is like naming a child. All of sudden the child arrives and parents need a name. Maybe they had one before the birth but it can go by the wayside when the child arrives.

The name has only four words and just 33 characters and hence 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 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 usually avoided.

**2. The study treatments**

When the UGDP started the characterization of diabetics was "juvenile" and "adult-onset"; 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 predominate treatment for type-2 diabetics was tolbutamide (Orinase®; marketed 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 without any long-term trials to establish long-term benefit.

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 getting 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	Plbo <sub>i</sub>	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)

The original cadre of clinics started enrollment in early 1961. Randomizations were by clinic, arranged in permuted blocks of 16 ensuring that after every sixteenth enrollment that there exactly the same number of persons assigned to each of the four treatment groups in the clinic.

By the time the treatments were set a new drug, 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 addition of the drug

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 ultimately the drug would 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. The option ultimately followed.

The treatment added are as listed below.

Phenformin	Phen	DBI-TD; 1 <sup>st</sup> week: one capsule/day (50mg) before breakfast; thereafter one capsule before breakfast and 2 <sup>nd</sup> capsule before evening meal
Placebo	Plbo <sub>p</sub>	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 marketing 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 almost perfect matches.

Phenformin and matching capsules were provided by the manufacturer.

Insulin was provided by Eli Lilly.

**3. Study sites**

The study involved 12 clinical centers. Originally five when the trial started; eventually 12 (two added in 1961, three in 1962, and two in 1963).

The coordinating center was originally located in the School of Public Health at the University of Minnesota. It was relocated to Baltimore in 1963.

	Institution	Location	Director	No. enrolled
Cl 1	Johns Hopkins School of Medicine (1960)	Baltimore, Md	Thaddeus Prout, MD	86
Cl 2	Massachusetts General Hospital (1960)	Boston, Mass	Robert Osborne, MD	86
Cl 3	University of Cincinnati Medical Center (1960)	Cincinnati, OH	Harvey Knowles, MD	90
Cl 4	University of Minnesota Hospitals (1960)	Minneapolis, Mn	Frederick Goetz, MD	94
Cl 5	The Jewish Hospital and Medical Center (1960)	Brooklyn, NY	Martin Goldner, MD	86
Cl 6	University Hospitals of Cleveland (1961)	Cleveland, OH	Max Miller, MD	78

	Institution	Location	Director	No. enrolled
Cl 7	Appalachian Regional Hospital (1961)	Williamson, W Va	Charles Jones, MD	94
Cl 8	University of Alabama Medical Center (1962)	Birmingham, Ala	Buris Boshell, MD	86
Cl 9	Presbyterian-St Luke's Hospital (1962)	Chicago, Ill	Theodore Schwartz, MD	80
Cl 10	Washington University School of Medicine (1962)	St Louis, Mo	William Daughaday, MD	79
Cl 11	University of Puerto Rico School of Medicine (1963)	San Juan, PR	Lillian Haddock, MD	91
Cl 12	The Virginia Mason Research Center (1963)	Seattle, Wa	Robert Reeves, MD	77
Total				1,027
CC	University of Mn School of Public Health (1960-63) University of Md School of Medicine (1963-74) Maryland Medical Research Institute (1974-81)	Minneapolis, Mn Baltimore, Md Baltimore, Md	Christian Klimt, MD Christian Klimt, MD, DrPH Christian Klimt, MD, DrPH	

**4. Enrollment and randomization design**

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 32<sup>nd</sup> person to the scheme involving administration of phenformin and its corresponding placebo.

	Plbo <sub>i</sub>	Tolb	IStd	IVar	Plbo <sub>p</sub>	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 reference (Gilbert et al; 1975).<sup>21</sup>

*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<sup>15</sup> were used for the treatment allocations in the first six clinics, and the Rand tables<sup>16</sup> 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 1STD 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.*

## **5. Data collection schedule**

The data collection schedule consisted of a qualifying baseline visit including a three hour glucose tolerance test (GTT). To be eligible persons had to have a sum blood GTT (fasting, 1, 2, and 3 hour values) of  $\geq 500$  mg./100 ml. The second visit one month later was when randomization took place. After randomization persons were counted as enrolled even if they never returned for followup visits. Persons 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 exam in quarter 1, heart exam in quarter 2, kidney exam in quarter 3, and peripheral vascular and neural examination in quarter 4 plus a glucose tolerance test (GTT). The sequence was repeated for each subsequent year of followup.

**Baseline and enrollment visit**

Baseline visit

Randomization (enrollment) visit

**Followup visits**

1st quarter (3, 15, ... mos after randomization): Physical and eye exam

2nd quarter (6, 18, ... mos after randomization): Physical and heart exam

3rd quarter (9, 21, ... mos after randomization): Physical and kidney exam

4th quarter (12, 24, ... mos after randomization): Physical and peripheral vascular and neural exam and GTT

**6. Results**

Of the four treatments tested only two, IVar and IStd, made it to the end, but without distinction. The two oral agents, tolbutamide and phenformin, were stopped early because of ill-effects.

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

**Tolbutamide result (UGDP, 1970e)<sup>63</sup>**

*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)<sup>57</sup>**

*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)<sup>51</sup>**

*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 creatine 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 microvascular 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).*

**7. Court battles**

The fun began with publication of the tolbutamide results in a supplement to Diabetes in November of 1970. Unbeknownst to us, the supplement also included a statement regarding 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 the Journal 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 diatheses. 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 the statements.

The Committee on the Care of the Diabetic (CCD) was formed the same month the results were published as a counter force to efforts to relabel or withdraw tolbutamide from the market.

The members of the CCD coordinating committee were:

**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, then expanded to blocking removal of phenformin from the market and to access to raw data from the trial.

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1970	November	Committee on the Care of Diabetic (CCD) formed
1971	June	FDA outlines labeling changes for sulfonylureas (FDA, 1971) <sup>20</sup>
1971	October 7	CCD petitions FDA commissioner to rescind proposed label change
1972	May	FDA reaffirms position on proposed labeling change (FDA, 1972a) <sup>19</sup>
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 (FDA, 1975) <sup>18</sup>
1972	August 3	Commissioner of FDA denies 13 July 1972 CCD request for evidentiary hearing (US Court of Appeals, 1973) <sup>42</sup>
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) <sup>42</sup>
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 (FDA, 1975; US Court of Appeals, 1973) <sup>18,42</sup>
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) <sup>42</sup>
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) <sup>42</sup>
1972	November 7	Preliminary injunction against proposed label change granted by United States District Court for the District of Massachusetts (FDA, 1975) <sup>18</sup>
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 (FDA, 1975; US Court of Appeals, 1973) <sup>18,42</sup>
1973	October	FDA hearing on labeling of oral agents (FDA, 1975) <sup>18</sup>
1974	February	FDA circulates proposed labeling revision (FDA, 1975) <sup>18</sup>
1974	March-April	FDA holds meeting on proposed label change, then postpones action on change until report of Biometrics Committee (FDA, 1975) <sup>18</sup>
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) <sup>46</sup>



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) <sup>45</sup>
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) <sup>45</sup>
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, 1975) <sup>41</sup>
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) <sup>44</sup>
1975	December	FDA announces intent to audit UGDP results (US Supreme Court, 1978) <sup>48</sup>
1976	February 5	United States District Court for the District of Columbia rules UGDP raw data not subject to FOIA (US District Court, 1976) <sup>40</sup>
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) <sup>48</sup>
1976	October	FDA Endocrinology and Metabolism Advisory Committee recommends removal of phenformin from market (FDA, 1977a) <sup>15</sup>
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) <sup>43</sup>
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 (FDA, 1977a) <sup>15</sup>
1977	May 6	FDA begins formal proceedings to remove phenformin from market (FDA, 1977a) <sup>15</sup>
1977	May 13	FDA holds public hearing on petition of HRG (FDA, 1977a) <sup>15</sup>
1977	July 25	Secretary of HEW announces decision to suspend New Drug Applications (NDAs) for phenformin in 90 days (FDA, 1977b) <sup>16</sup>
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	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 (FDA, 1977d) <sup>17</sup>
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) <sup>39,48</sup>
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) <sup>48</sup>
1978	October 17	Petition for rehearing at the United States Court of Appeals for the District of Columbia Circuit denied (US Supreme Court, 1978) <sup>48</sup>
1978	November 14	Results of FDA audit of UGDP announced (FDA, 1978) <sup>14</sup>
1978	November 15	FDA Commissioner orders phenformin withdrawn from market
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) <sup>48</sup>
1979	April 10	Appeal of October 21, 1977 ruling denied†
1979	May 14	Writ of certiorari granted
1979	October 31	UGDP case of Forsham et al., versus Harris et al., argued before the United States Supreme Court (US Supreme Court, 1980) <sup>47</sup>

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1980	March 3	United States Supreme Court holds that HEW need not produce UGDP raw data; 7 to 2 decision (US Supreme Court, 1980) <sup>47</sup>
1984	March 16	Revised label for sulfonylurea class of drugs released (FDA, 1984a; 1984b; 1984c) <sup>11,12,13</sup>

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

Members of the CCD regarded the UGDP as badly flawed and reasoned that if they were to gain access to raw data of the trial they would be able to reanalyze and show where we went wrong. They wanted data forms transmitted to the Coordinating Center from study clinics and computer tapes used in the Coordinating Center for data analysis.

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 one from the Military Audit Project (28 December 1976) and one from the Reporters Committee for Freedom of the Press (13 January 1977). Those two requests were for all telephone notes while Kissinger was Secretary of State.

Safire's request was denied on grounds that Kissinger was National Security Adviser during the time period covered in his request and that advisers to the President are not considered to be governmental agencies under the 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 majority opinion was written by Rehnquist with Burger, White, and Powell joining. Brennan and Stevens filed opinions concurring in part and dissenting in part with Rehnquist. Justices Marshall and Blackmun did not take part in the consideration or decision of the cases.

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 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](http://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. It is apparent that the ruling might well have been different if the trial was done under contract with the NIH and subjected to closer monitoring by the agency.

### 8. Lessons

Ask people who have been involved in trials and they almost always mark their involvement as a great learning experience. No exception for me. The UGDP was my first venture into trials. The only thing I knew about trials when signing on with Chris Klimt was what I read in textbooks.

#### **Publish first, present later**

UGDP investigators, early on, agreed to a "publish first, present later" policy in regard to primary results from the trial. The first test of that policy came with the decision to stop the tolbutamide treatment. However, as often happens, there is backsliding when faced with reality.

Ultimately, investigators 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)<sup>59,60,61</sup> 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 Diabetes. 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 appeared in print in November, about five months after the presentation in St. Louis. The intervening time meant that investigators stood helpless in answering the deluge of criticism until the papers were published. The time gap was problematic. Diabetologists were deluged by calls from worried patients concerning the drug they were on. The fact that clinicians had to answer patients questions without benefit of a publication 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 no point in reading the published results.

**Lesson:** Publish first! Present later.

### **Trust but verify**

Persons had to have a sum blood glucose tolerance test of  $\geq 500$  mg/100 ml to be eligible for enrollment. (UGDP, 1970d)<sup>62</sup> The test consisted of an overnight fasting value plus 1, 2, and 3 hour post-glucose challenge values.

Glucose determinations were to be done locally. There had been discussion of 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 regarding their method for determining glucose levels during an investigators meeting. 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 affected determinations for 280 patients.

The mistake required converting 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 corrected sum GTTs below the diagnostic cut point of  $\geq 500$  mg/100 ml. (UGDP, 1970d)<sup>62</sup>

**Lesson:** It is not sufficient to specify requirements in the study protocol. One must also check that the requirements are satisfied.

### **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 form changes and revisions 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 ultimately got out numbered and overrun. The changes could range from being as trivial as correcting spelling errors to as major as changing the order of items on a form or adding new sections to a form.

**Lesson:** Delete the word "final" from your vocabulary when it comes to data collection forms and protocols. Use version numbers instead 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 results are published and the world does not like them, people can always come up with some baseline variable that investigators failed to collect and attribute the difference to that variable. That was the case with critics of the UGDP with regard to 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 landscape with regard to 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.

Investigators did, in fact, make an effort to rectify the oversight around 1972 with the collection of retrospective smoking histories. There were no major differences among the treatment groups with regard to smoking history. However, the results were never published because of questions involved in constructing baseline smoking histories long after patients were enrolled and use of surrogate respondents for deceased patients.

**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 dropout, so that one can classify persons as to whether alive or dead at analysis time. 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 persons lost to followup 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 no one paid attention to that requirement. Hence, when it came time to produce the publication describing the tolbutamide mortality results, nine years after the start of enrollment, investigators had 23 dropouts in the tolbutamide-assigned group of patients and 24 in the placebo-assigned group with unknown vital status. 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 locate dropouts to determine if they were alive or dead.

Ultimately, via those efforts, investigators were able to determine the vital status of everyone enrolled, except for five; one person assigned to the tolbutamide treatment group, two persons assigned to the placebo treatment group, and the other two persons assigned to the insulin-variable treatment group.

The hard core unlocatables included a person by the name of Wong who moved to Chinatown in San Francisco. He was lost among 100s of Wongs in Chinatown.

**Lesson:** Keep the "locator information" current and engage in efforts to locate people lost to followup at yearly intervals to be ready for a stop whenever it may come.

### Who said you can vote?

There came that fateful day 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 the center directors and one vote for deputy directors) – but without any clear policy on proxy votes, “stand in” voters in the absence of the director or deputy director, or the designation, “deputy director.” The ambiguities were noted when the policy was drafted, but considered not important because voting would be unnecessary in the expectation that major decisions would be by “consensus”.

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

**Lesson:** The time to figure out who has a vote is before there are issues to vote. 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 after enrollment was at three month intervals over the course of followup. 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 people missed a visit.

Suppose a person does not show up for the 6 month visit, but does for the 9 month visit, i.e., the second followup 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 as an FU 3 and others did the heart exam and labeled it as an FU 2 visit. 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 antihyperglycemic 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 the trial was 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 the 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 power 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 persons 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.

*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 were patients told about the reason for stopping?*

The truth if they asked.

*What should happen to patients after the stop?*

Followup 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 followup visit 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.

### Dealing with brick baths

The investigators plan was "mum's the word" in regard to tolbutamide results until they were published. But the plan fell apart when investigators decided to present the results at the ADA 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 investors of results adverse to Upjohn. That the first report was on a financial service wire was no surprise in retrospect in view of the volume of sales due to uses of Orinase. The drug accounted for nearly half of all prescriptions for oral hypoglycemic agents at the time.(Meinert and Tonascia, 1986)<sup>30</sup>

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, 1970b; Schmeck, 1970)<sup>23,32,33,31</sup> 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 was at the time was to magazines at check out counters in supermarkets, always on the front page. Sample headlines below.

**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 in regard to the throwaway press.

A more difficult question was what to do about criticisms published in peer reviewed journals. There were several over the years, starting with Schor's,(1971)<sup>34</sup> and Feinstein's (1971)<sup>10</sup> in 1971, then Seltzer's in 1972<sup>37</sup>, Feinstein's again in 1976 (1976a; 1976)<sup>8,9</sup>, Kilo's et al in 1980<sup>22</sup> and others since. Most of these we answered. Responses are contained in references (UGDP, 1972<sup>56</sup>, Schwartz, 1971 and Schwartz and Meinert, 2004)<sup>35,36</sup> and an article by Cornfield (1971).<sup>5</sup>

**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)<sup>63</sup> 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).<sup>53</sup> The final publication in 1982 (UGDP, 1982)<sup>51</sup> 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 followup data for all study patients were deposited at the National Technical Information Service in 1983 (UGDP, 1983a, 1983b).<sup>49,50</sup>

**Lesson**

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

**After the fact consents**

Institutional Review Boards (IRBs) did not exist when the UGDP started. There were no consent forms for patients to read and sign. Whatever persons were told about what they were being approached for was up to clinic personnel.

In reality, the requirement for informed consents as a condition for researching on human beings existed long before the start of the UGDP. The requirement is the first item in a ten point manifesto growing out of the Nuremberg war crimes trials and known as the Nuremberg War Code, promulgated in 1947 (Shuster, 1997)<sup>38</sup>.

*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.*

Crofton (2006)<sup>6</sup> in a piece entitled *The MRC randomized trial of streptomycin and its legacy: A view from the clinical front line* indicated in regard to persons enrolled in the trial that “Neither group of patients knew that they were in a trial, which remained confidential throughout its 15 month duration”.

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 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 without their consents. Among them, one involving infecting "mentally defective" children in the Willowbrook State Hospital in New York with hepatitis and another involving 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)<sup>1</sup> focused attention on the issue of ethics in clinical research.

The outrage led to the Surgeon General of the USPHS to announce, 8 February 1966, that henceforth NIH grantees would have to provide evidence of procedures and practices designed to ensure documented informed consents in order to receive funding. The order and implementation of it eventually led to the creation of institutional review boards.

The problem for UGDP investigators was that the order came about when enrollment was finished. 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 consenting.

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

### **The label change**

The tolbutamide-placebo difference in CV 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 CV risks associated with 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 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 via a request to the Commissioner of the FDA (7 October 1971) to stay the relabeling. A stay was granted 7 November 1972.<sup>18</sup> The label had been printed and supplied to manufacturers when the stay was granted.



It was 13 years after relabeling was proposed before it was 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 onto other drugs not of the sulfonylurea class.

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

## 9. Reflections

The third aim of the UGDP was “development of methods applicable to cooperative clinical trials”. (The reference is to multicenter trials but the term of art then was “cooperative” but the better term is multicenter because all trials are cooperative even if not multicenter.<sup>27</sup>)

The UGDP was an early multicenter trials but, by no means the first. It was preceded by several, notably the Medical Research Council's multicenter TB streptomycin<sup>25</sup> trial and the Salk polio vaccine trials (Dawson, 2004)<sup>7</sup> to name just two. Hence, it is impossible to say what was borrowed from processors trials and was contributed by the UGDP.

Most of its contributions are in lessons learned from mistakes and early stops.

Investigators when they start a trial expect to carry it to its normal end. They are familiar with the problems that they may have recruiting but rarely face the possibility of stopping early.

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 it was not clear who in the investigator group 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 treatment results.

The practice of monitoring and reporting to the steering committee in relation to its semiannual meeting was well established when the mortality trend against the tolbutamide treatment group began to emerge. At first the trend was just a matter of curiosity but 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 also monitored results to decide if treatments should continue. He regarded investigator involvement as constituting a conflict of interest.

The issue raised ultimately led the NIH to require monitoring bodies for multicenter trials they fund:

*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 the monitoring body 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 sand traps in the data better than their external counterparts.

Even worse is the tendency to mask the monitors to treatment assignment, again because of the desire to avoid bias that may creep in if the committee knows treatment assignment. That practice is what led me to write, years back, “Masked monitoring, blind stupidity?” (Meinert, 1998).<sup>29</sup>

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